Skin Cancer/Sunscreen -- the Dilemma

UCSD Department of Family
and Preventive Medicine

Vitamin D Workshop

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DISCLOSURES

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose.

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Objectives

Describe the epidemiology of cutaneous malignant melanoma in terms of:

- Person, Place, and Time

Identify risk factors for melanoma

- Individual and behavioral characteristics
- Environmental risk factors

Differentiate between two kinds of ultraviolet irradiance:

- UVA and UVB

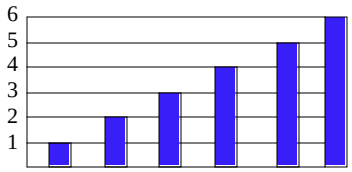
Understand the difference between primary and secondary prevention of melanoma

Make recommendations for primary prevention of melanoma based on its epidemiology

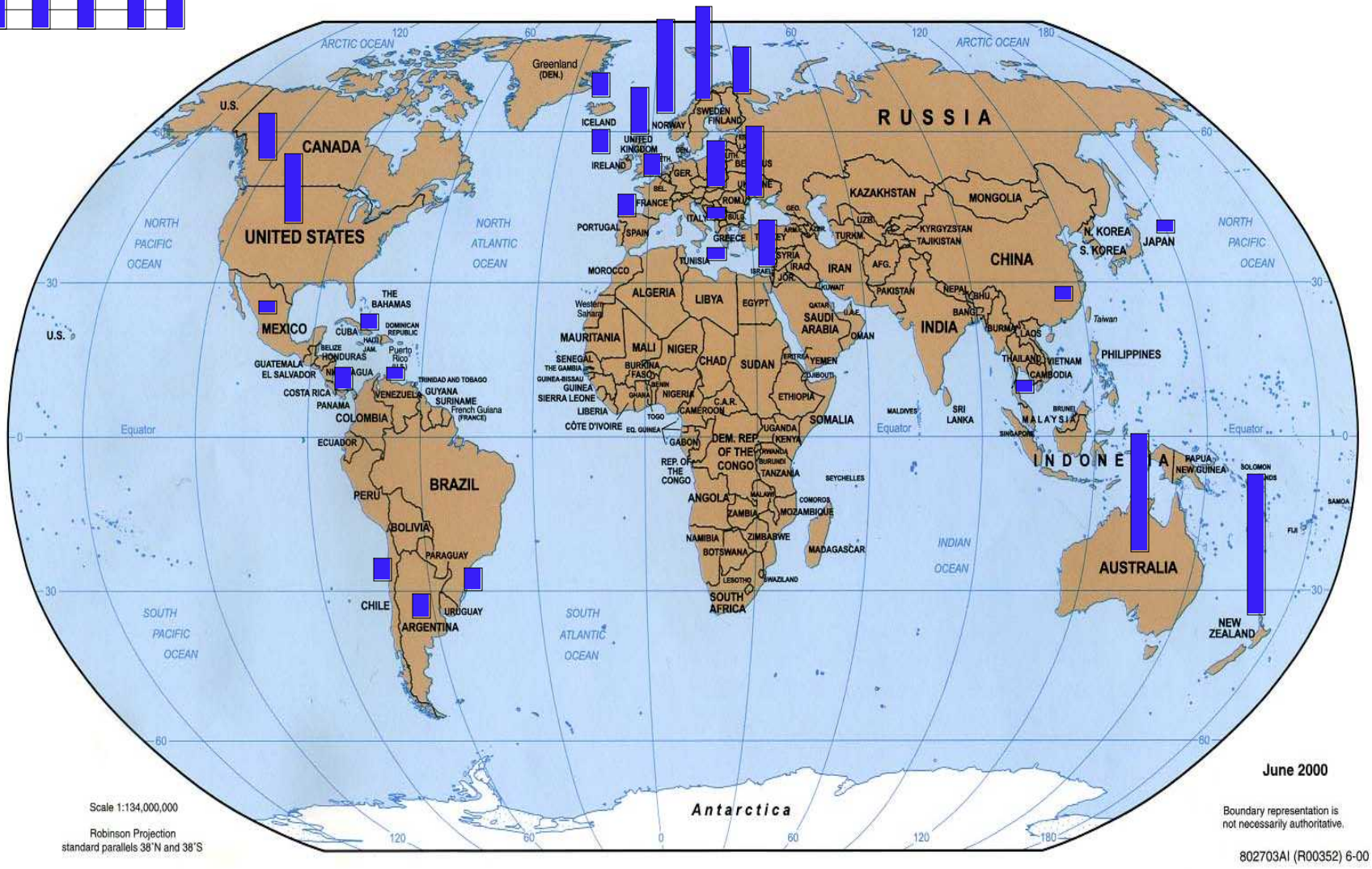
Screening: Secondary Prevention

ABCD screening guidelines:

Asymmetry - uneven in shape or color
Border - is irregular
Color - flag sign is a mole that has red, white, and blue colors
Diameter-increases or is greater than 6 millimeters



Melanoma: Person and Place

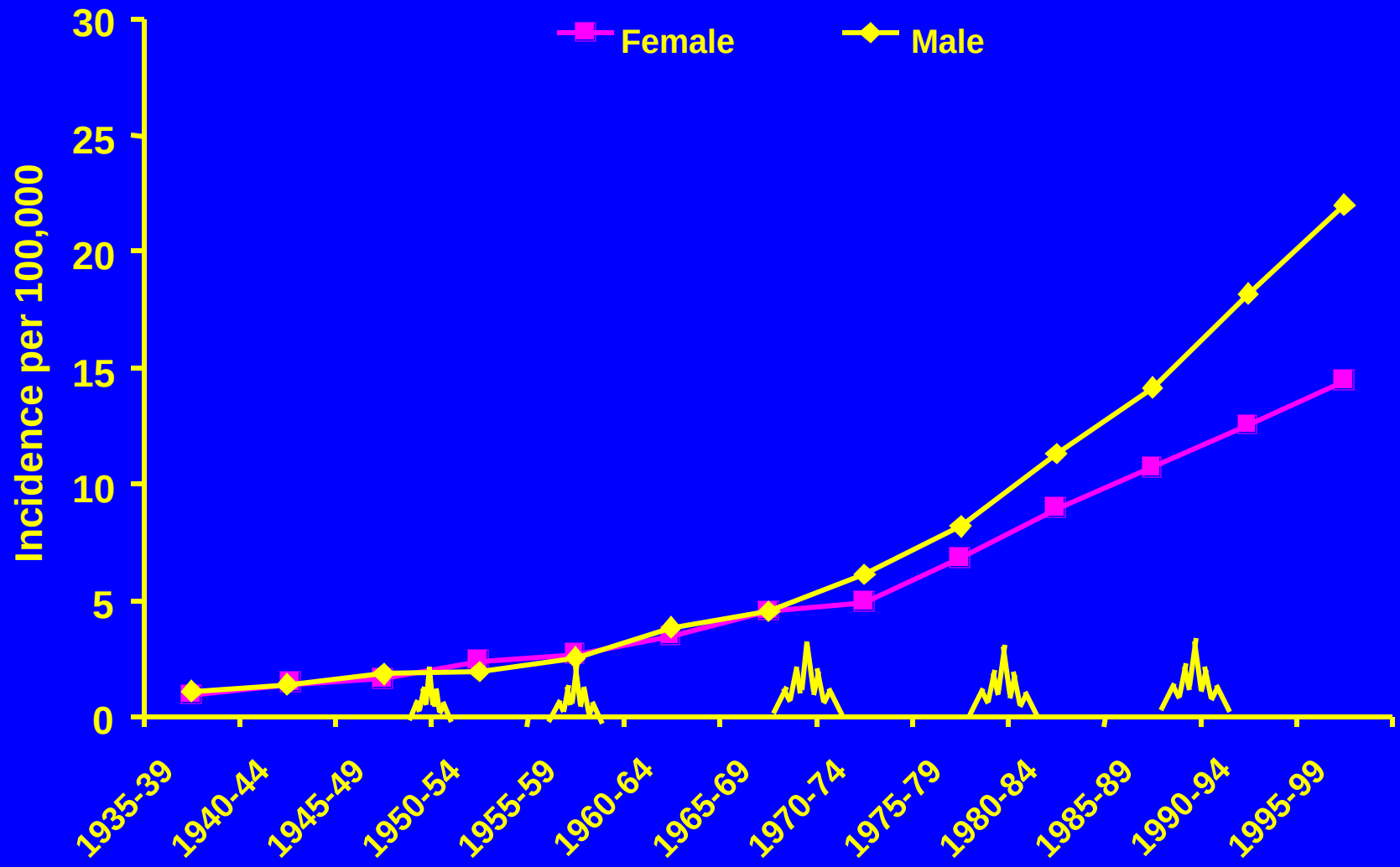


Age-adjusted melanoma mortality rates in men, 2002

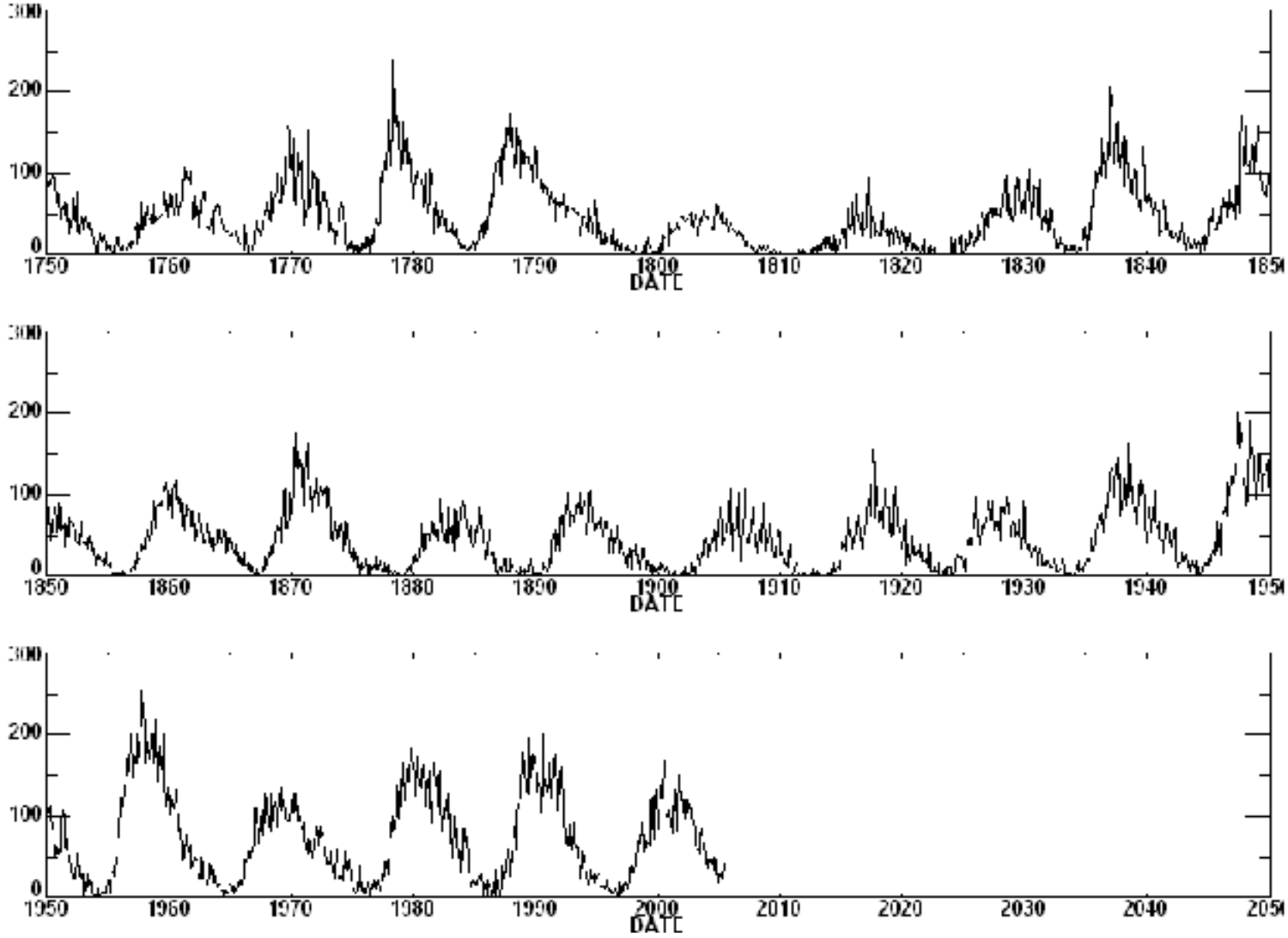
Global burden 160,000 cases, 41,000 deaths, both sexes

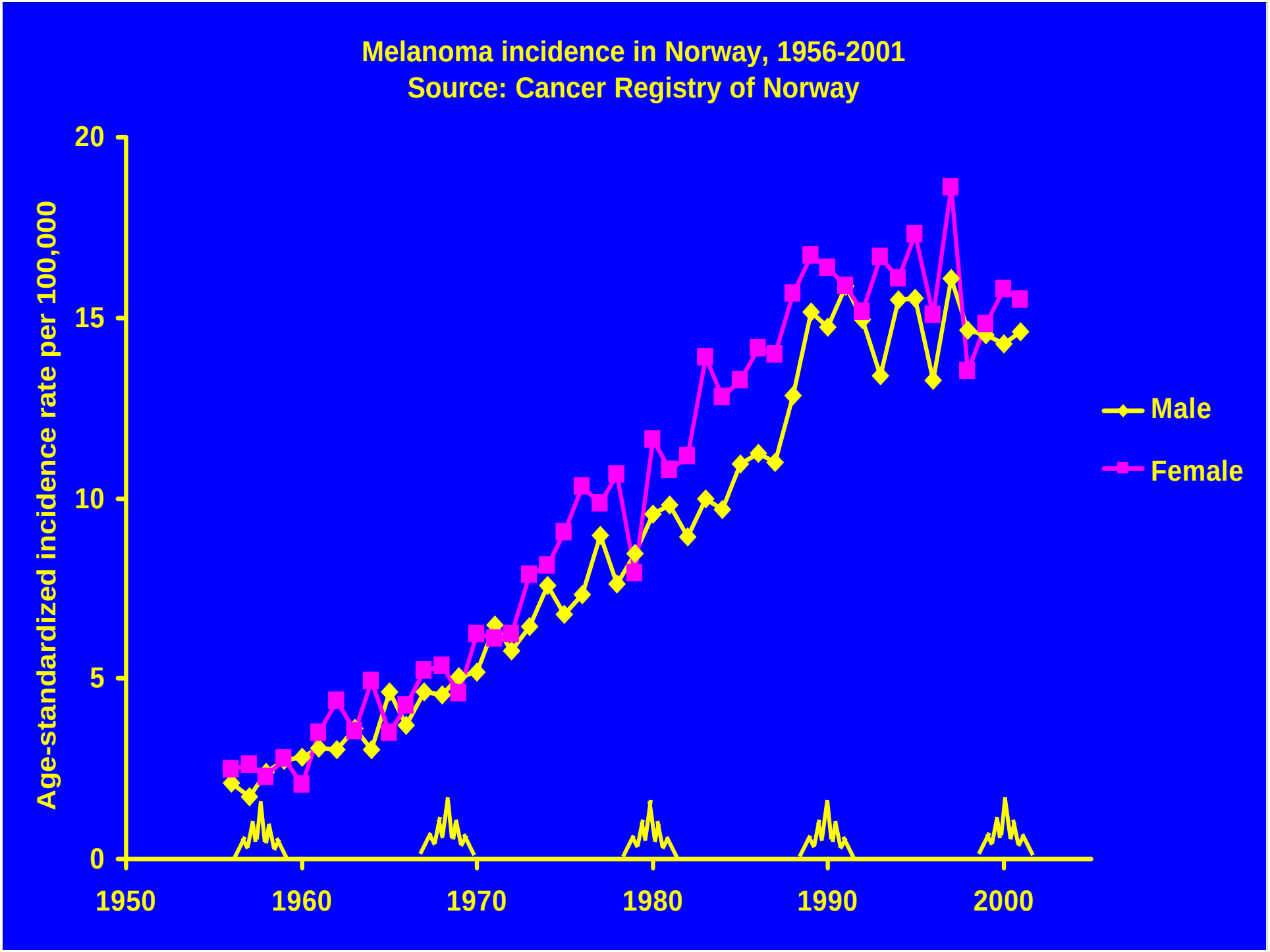
Melanoma: Place and Time

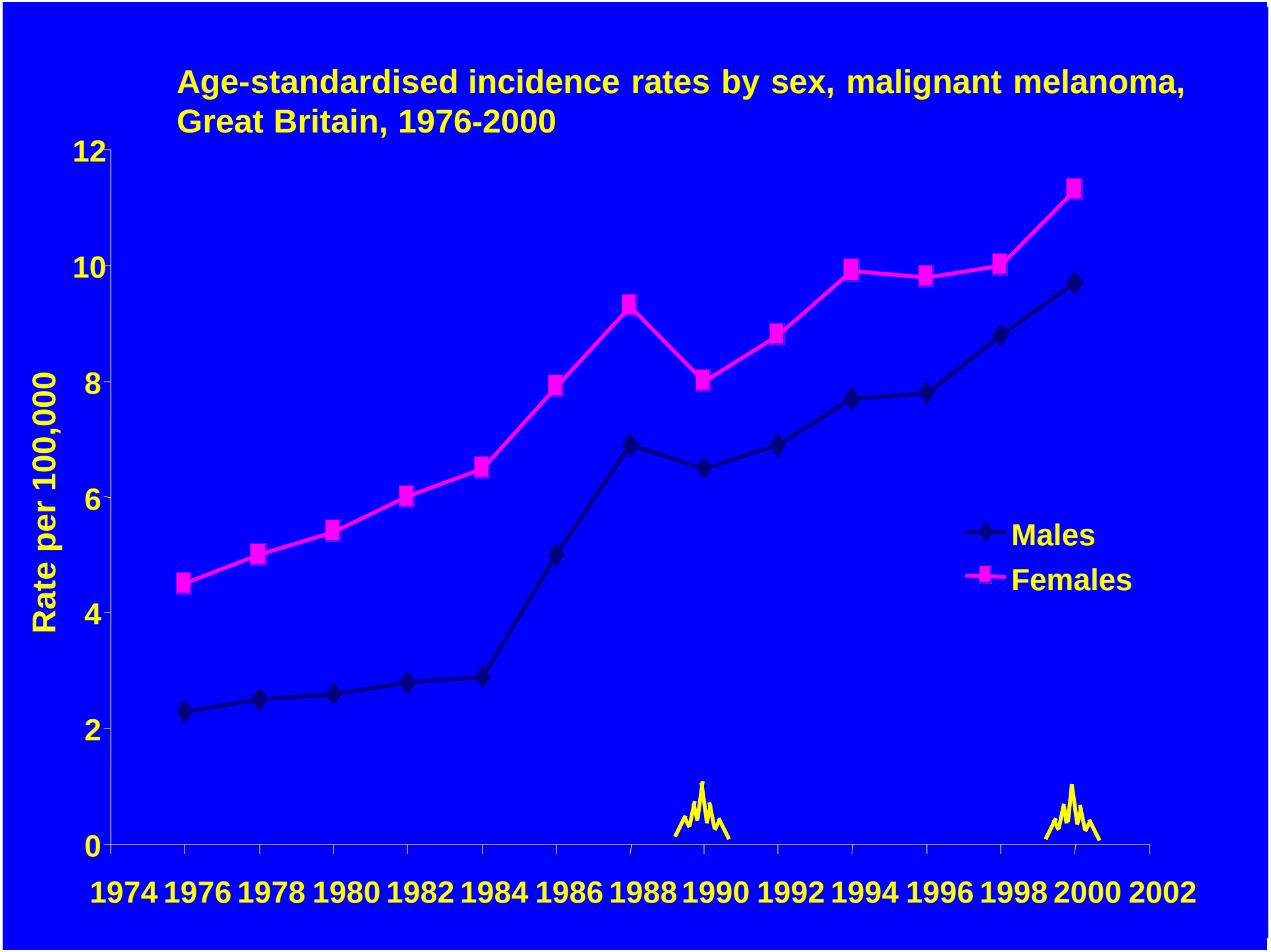
Melanoma incidence in Connecticut, 1935-1999
Source: Connecticut Tumor Registry

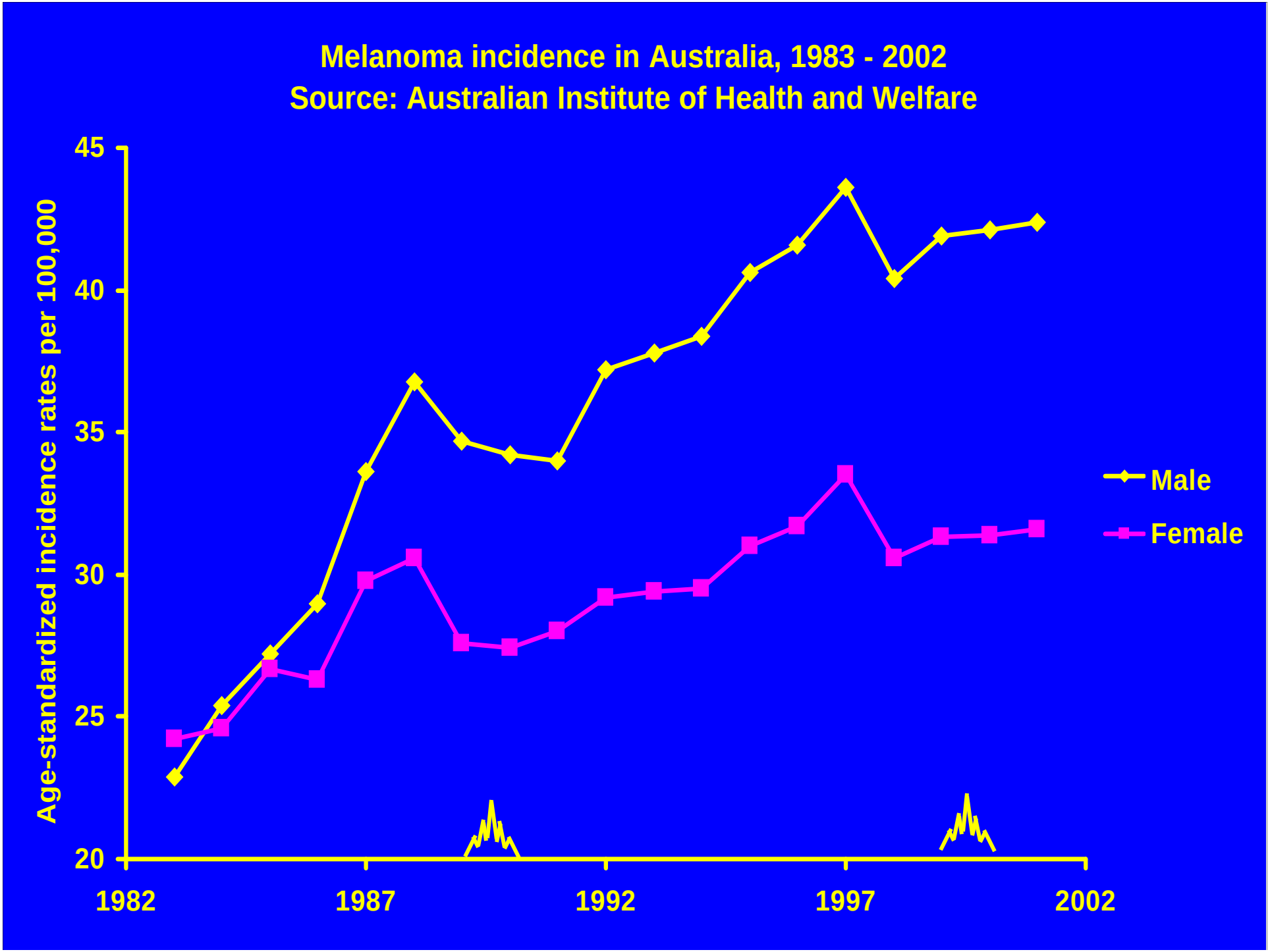


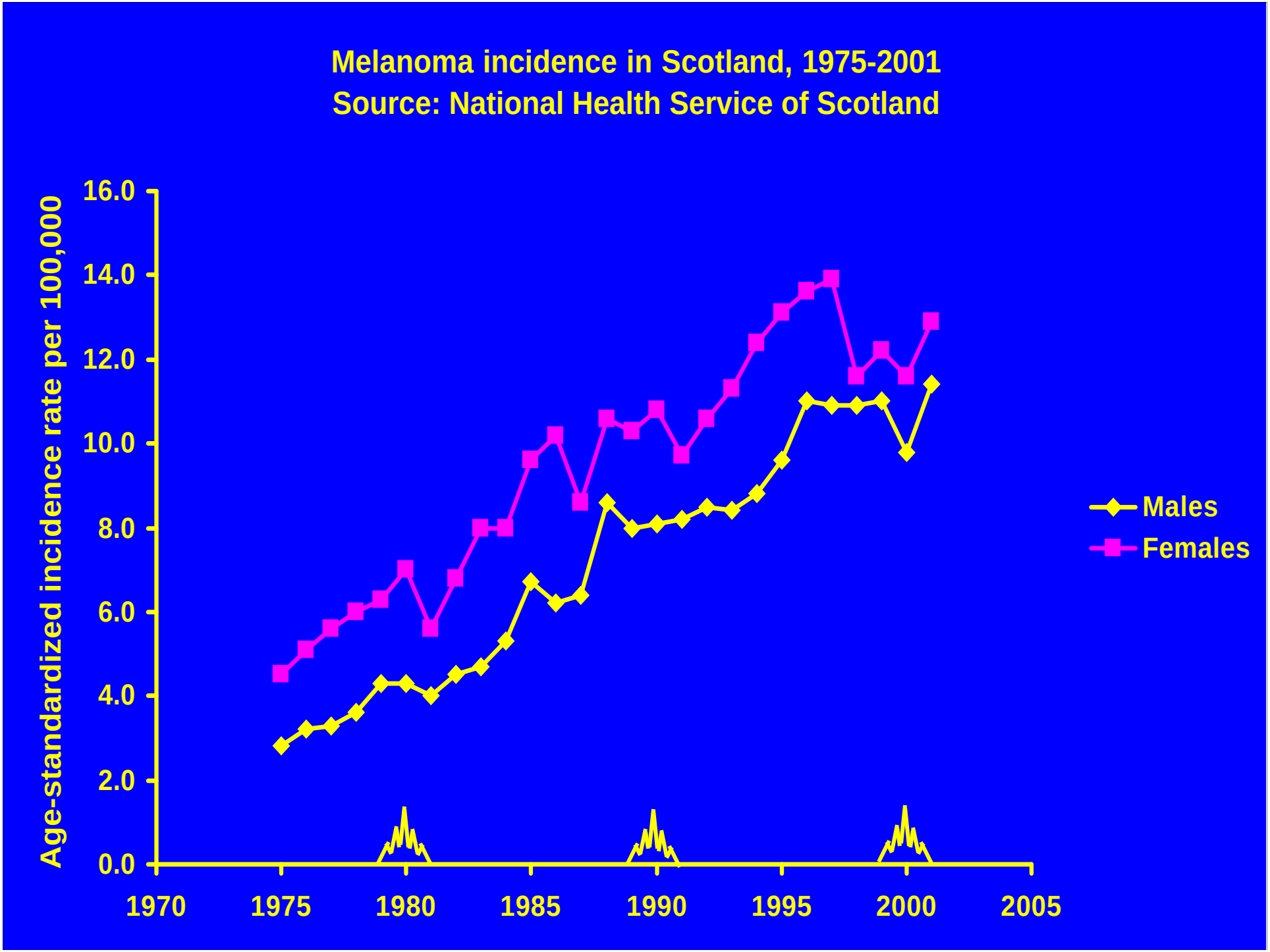
Monthly Average Sunspot Number, 1750-2005

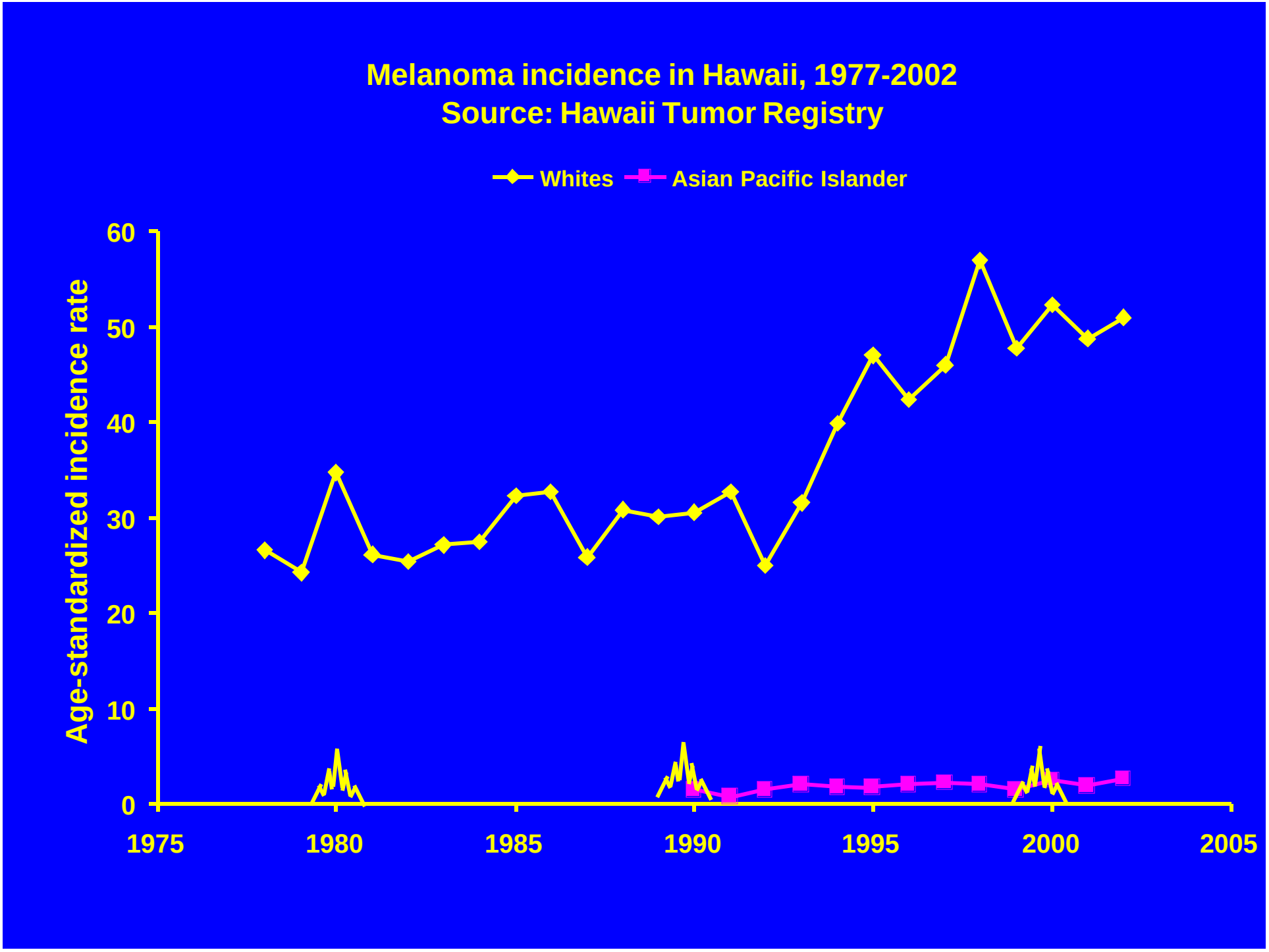


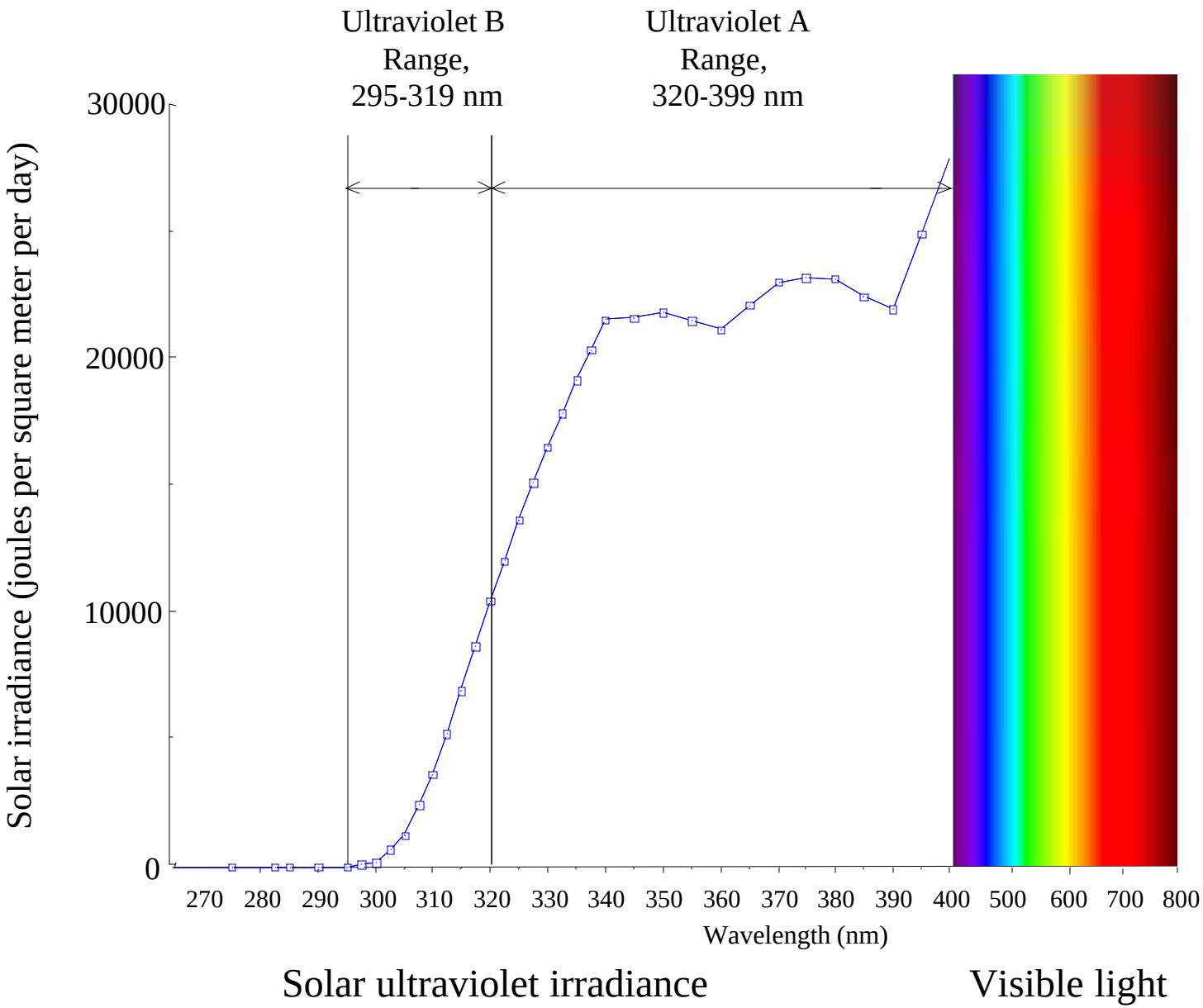

Melanoma incidence in Norway, 1956-2001
Source: Cancer Registry of Norway
Age-standardized incidence rate per 100,000
20
15
10
5
0
1950
1960
1970
1980
1990
2000
Male
Female


Age-standardised incidence rates by sex, malignant melanoma, Great Britain, 1976-2000
Rate per 100,000
0
2
4
6
8
10
12
1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002
Males
Females

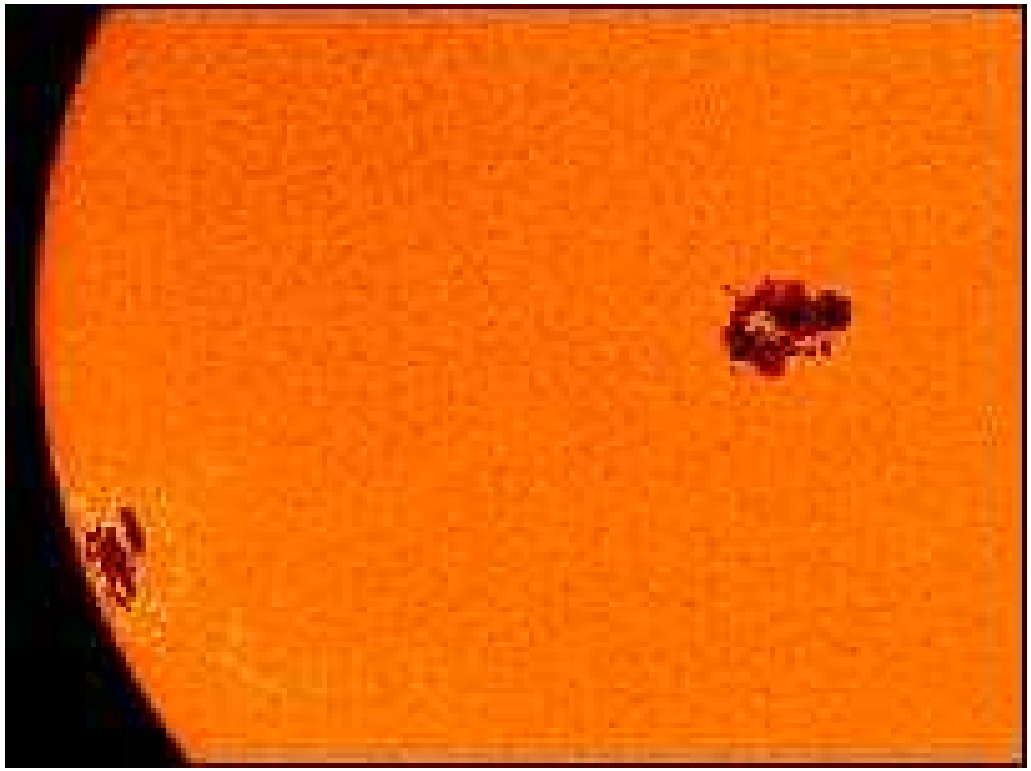

Melanoma incidence in Australia, 1983 - 2002
Source: Australian Institute of Health and Welfare
Age-standardized incidence rates per 100,000
45
40
35
30
25
20
1982
1987
1992
1997
2002
Male
Female


Melanoma incidence in Scotland, 1975-2001
Source: National Health Service of Scotland
Age-standardized incidence rate per 100,000
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
1970
1975
1980
1985
1990
1995
2000
2005
Males
Females


Melanoma incidence in Hawaii, 1977-2002
Source: Hawaii Tumor Registry
Whites
Asian Pacific Islander
Age-standardized incidence rate
60
50
40
30
20
10
0
1975
1980
1985
1990
1995
2000
2005

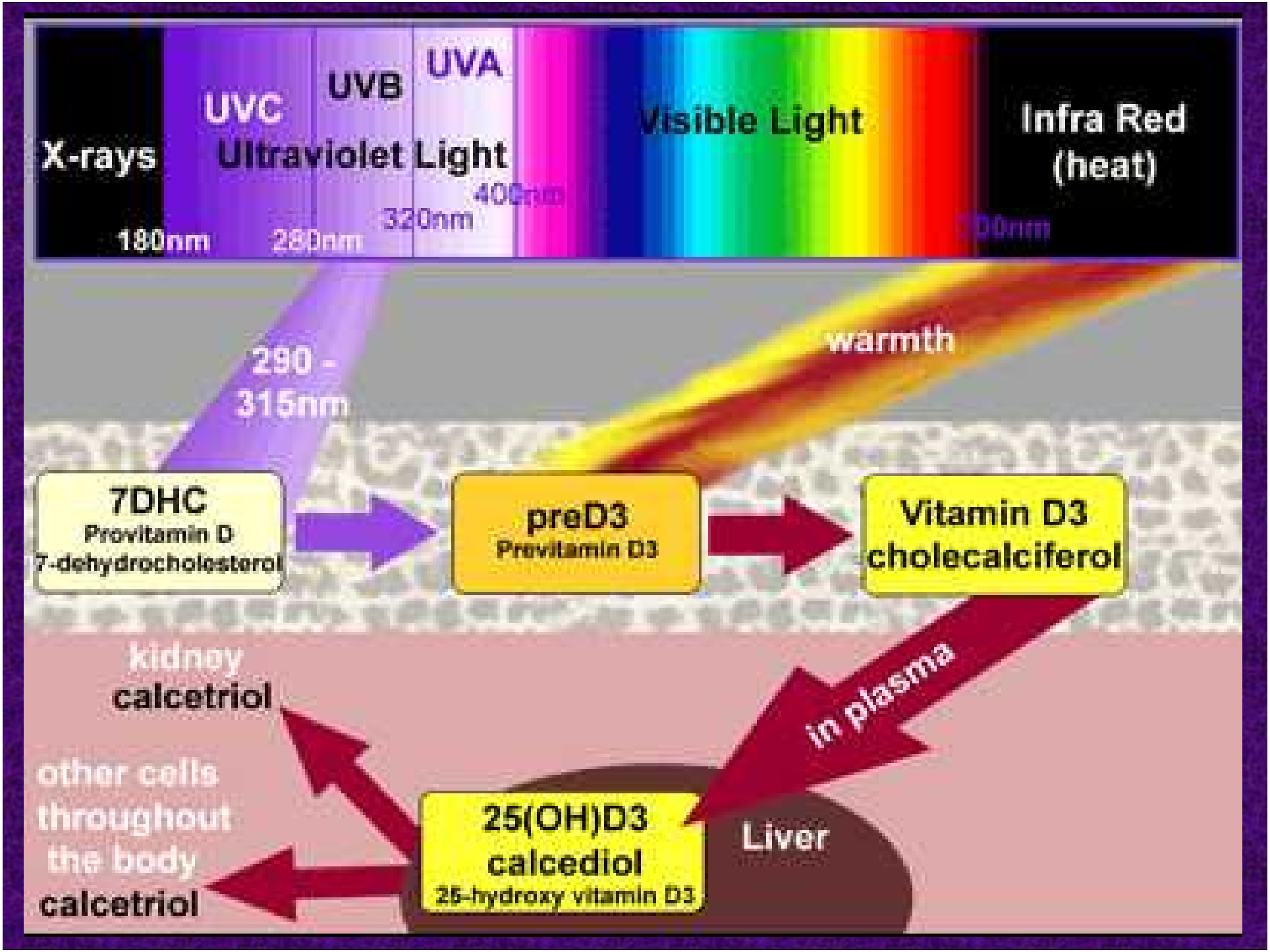

Ultraviolet B Range, 295-319 nm
Ultraviolet A Range, 320-399 nm
Solar irradiance (joules per square meter per day)
30000
20000
10000
0
270 280 290 300 310 320 330 340 350 360 370 380 390 400 500 600 700 800
Wavelength (nm)
Solar ultraviolet irradiance
Visible light

Role of UVB in Vitamin D Synthesis



The sun is the source of UVB used to make vitamin D. (Photo: Stanford Univ.).
Less than 1% of solar radiation is UVB.

Four UVB photons combine with one molecule of cholesterol (7DHC)
Opens a ring to make previtamin D
Warmth converts to vitamin D in skin (chlocalciferol)


X-rays
UVC
UVB
UVA
Ultraviolet Light
Visible Light
Infra Red
(heat)
180nm
280nm
320nm
400nm
700nm
290 -
315nm
warmth
7DHC
Provitamin D
7-dehydrocholesterol
preD3
Previtamin D3
Vitamin D3
cholecalciferol
kidney
calcetriol
in plasma
other cells
throughout
the body
calcetriol
25(OH)D3
calcediol
25-hydroxy vitamin D3
Liver

Laboratory Studies

In vitro studies find that vitamin D is a potent antiproliferative agent against various tumor cells including malignant melanoma [1]

25 (OH) vitamin D (calcidiol) or 1,25 $(OH)_2$ vitamin D (calcitriol) inhibited growth in a human melanoma cell line (ME18) to approximately 60 percent [2]

Studies have found a dose- and time- dependence of this anti-proliferative effect [2]

1) Pelczynska M, Switalska M, Maciejewska M, Jaroszewicz I, Kutner A, Opolski A. Antiproliferative activity of vitamin D compounds in combination with cytostatics. *Anticancer Research* 2006;26:2701-5

2) Gruber BM, Anuszewska EL. Influence of vitamin D3 metabolites on cell proliferation and cytotoxicity of adriamycin in human normal and neoplastic cells. Toxicol In Vitro. 2002;16:663-7.

Sun exposure is associated with increased survival from melanoma

Solar elastosis (present versus absent) was associated with a 60% increase in survival in patients with malignant melanoma (HR = 0.4, 95% CI = 0.2 to 0.8, P = 0.009)

Sunburn and history of high intermittent sun exposure were also statistically significantly inversely associated with death from melanoma

Source: Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, Barnhill R. Sun exposure and mortality from melanoma. J Natl Cancer Inst. 2005;97:195-9.

Vitamin D and melanoma

Vitamin D Quintile	Vitamin D Intake	Melanoma cases	Controls	Total
Highest	> 158 IU	84	112	196
Lowest	< 58 IU	120	112	232
Total		204	224	428

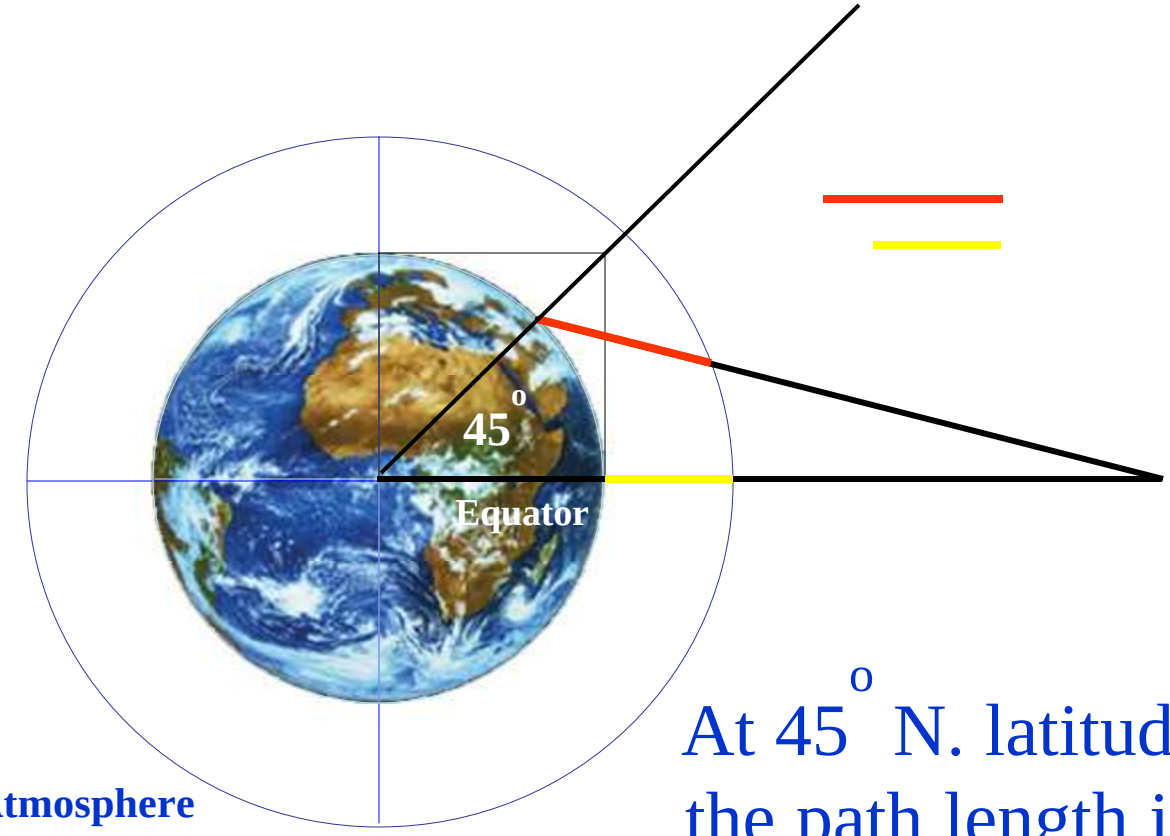
Odds ratio = 0.67 *p*-value < 0.05 *p*-value for trend =0.03

Adjusted* Odds ratio = 0.61 (95% CI =0.40-0.95) *p*-value < 0.05

* Adjusted for age, race, sex, study site, number of nevi, and skin response.

†Source: Millen AE, Tucker MA, Hartge P, et al. Diet and melanoma in a case-control study. Cancer Epidemiol Biomark Prev 2004;13:1042-51.

UVB varies by Solar Angle which changes with Season, Latitude, and Time of Day



Atmosphere not to scale

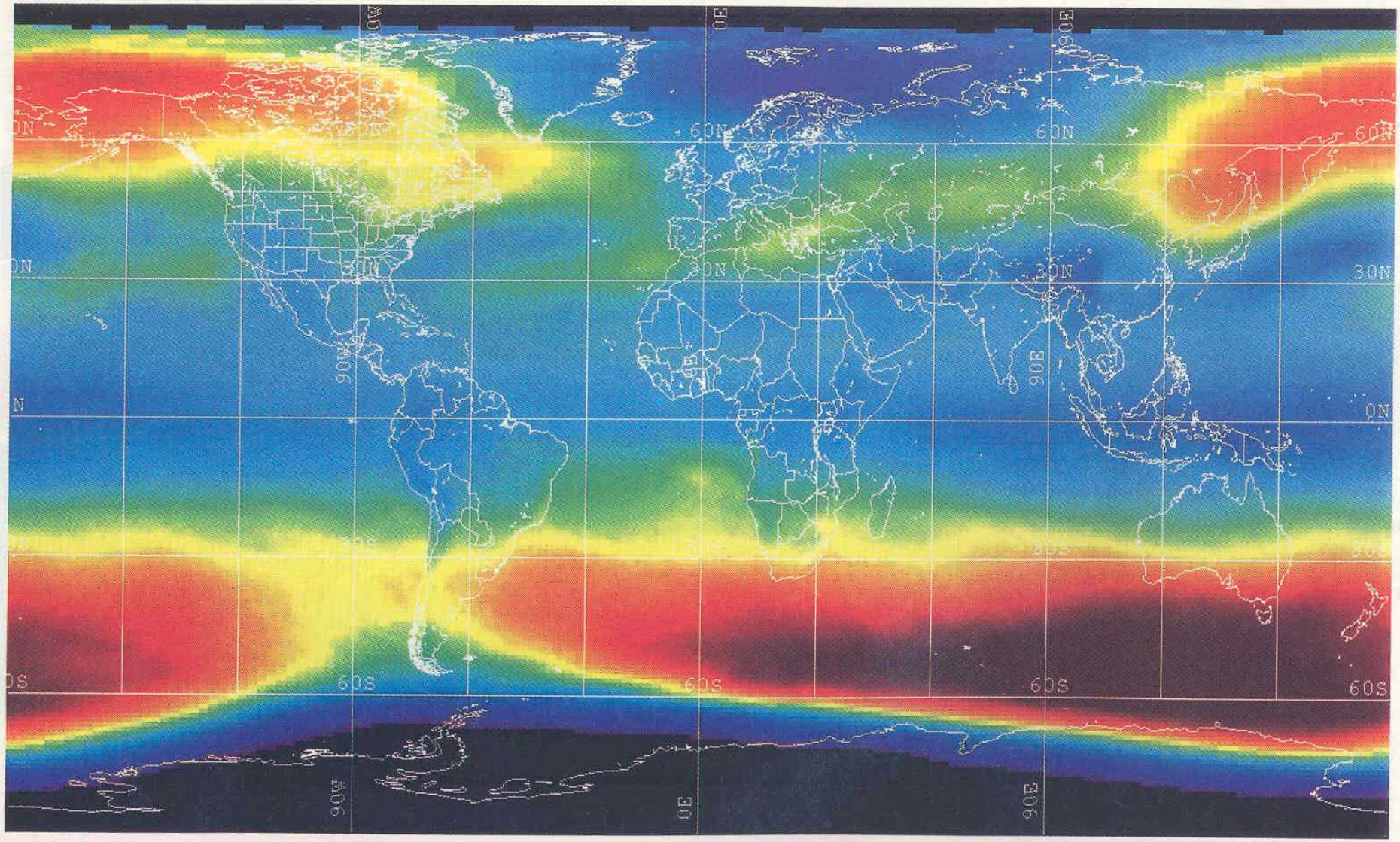
The flashlight beam model

Oblique Rays

Perpendicular Rays

At 45° N. latitude on an equinox the path length is approximately 40% longer then at the equator

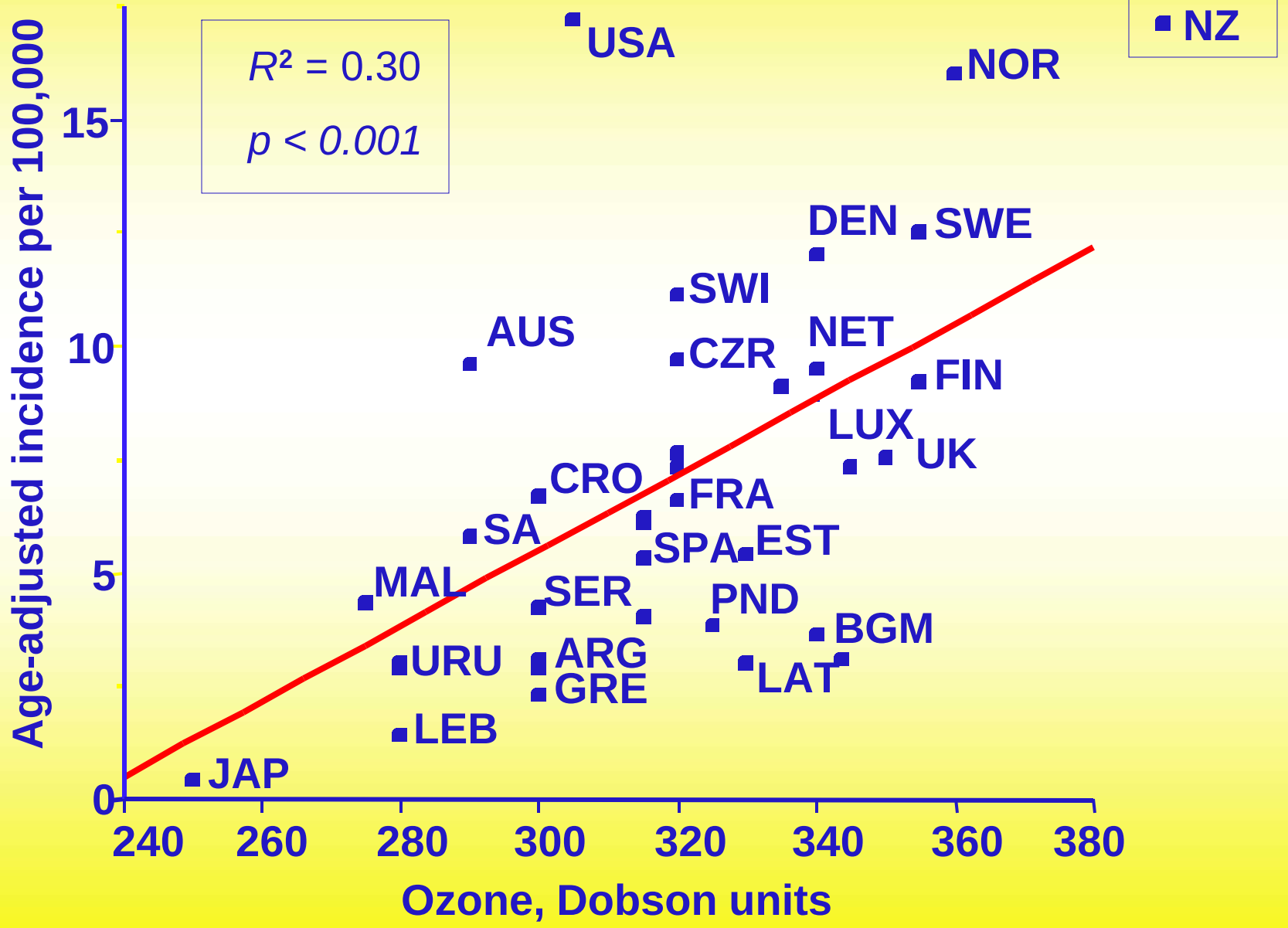
B. OCTOBER 1989



Total Column Ozone (Dobson units)

Age-adjusted melanoma incidence rates per 100,000 by stratospheric ozone thickness, 36 industrialized countries

Sources: Ozone, NASA TOMS; Incidence, IARC 2002



Ozone, pigmentation, and melanoma

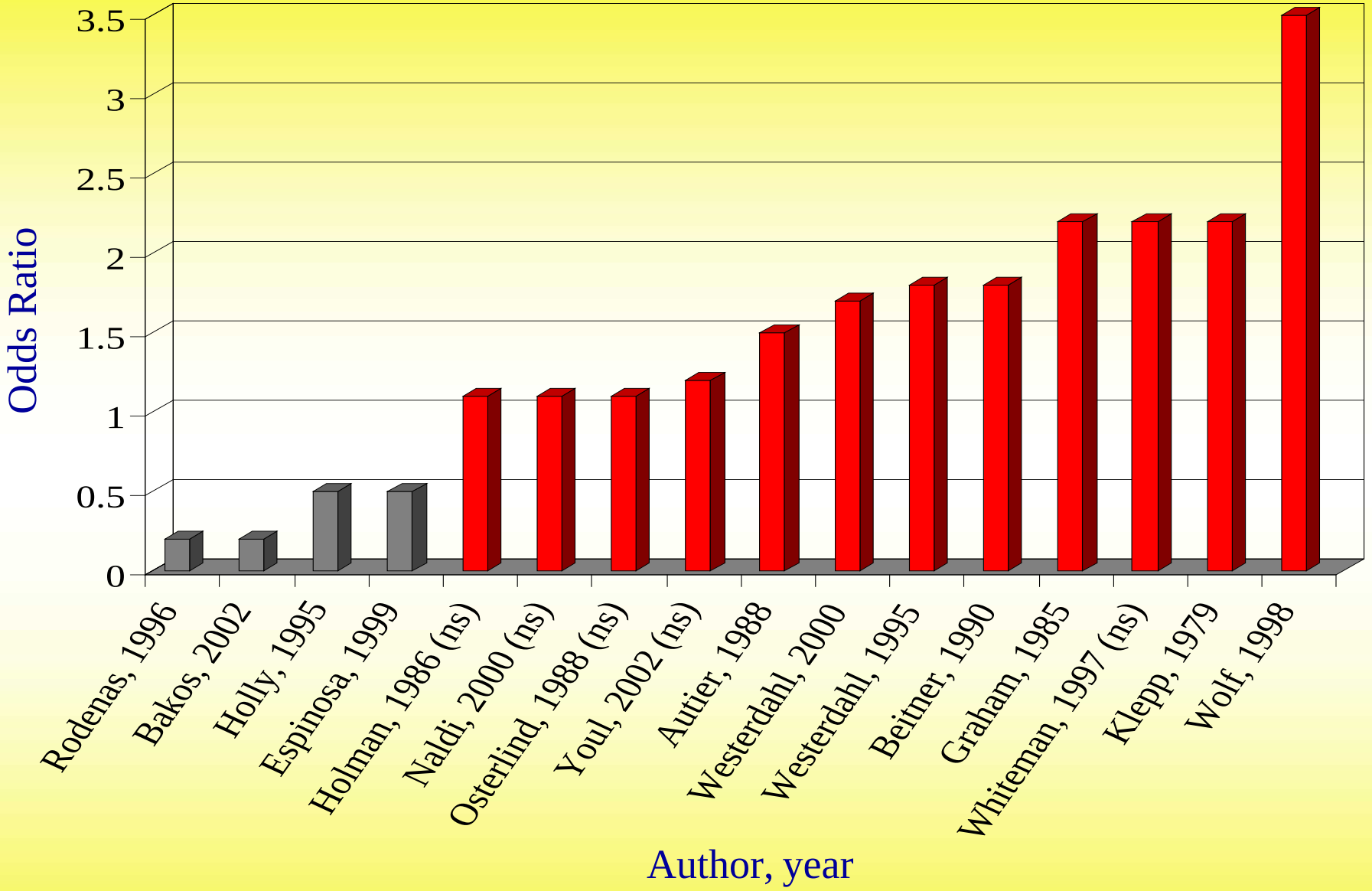
Variable	Regression coefficient	Standard error	*t*	*p*
Ozone*	0.0346	0.0064	5.34	< 0.0001
Pigmentation†	-0.9838	0.2622	-3.75	0.0002

$R^2 = 0.43,\ p < 0.0001$

*Ozone in Dobson units. Source: NASA TOMS Satellite package

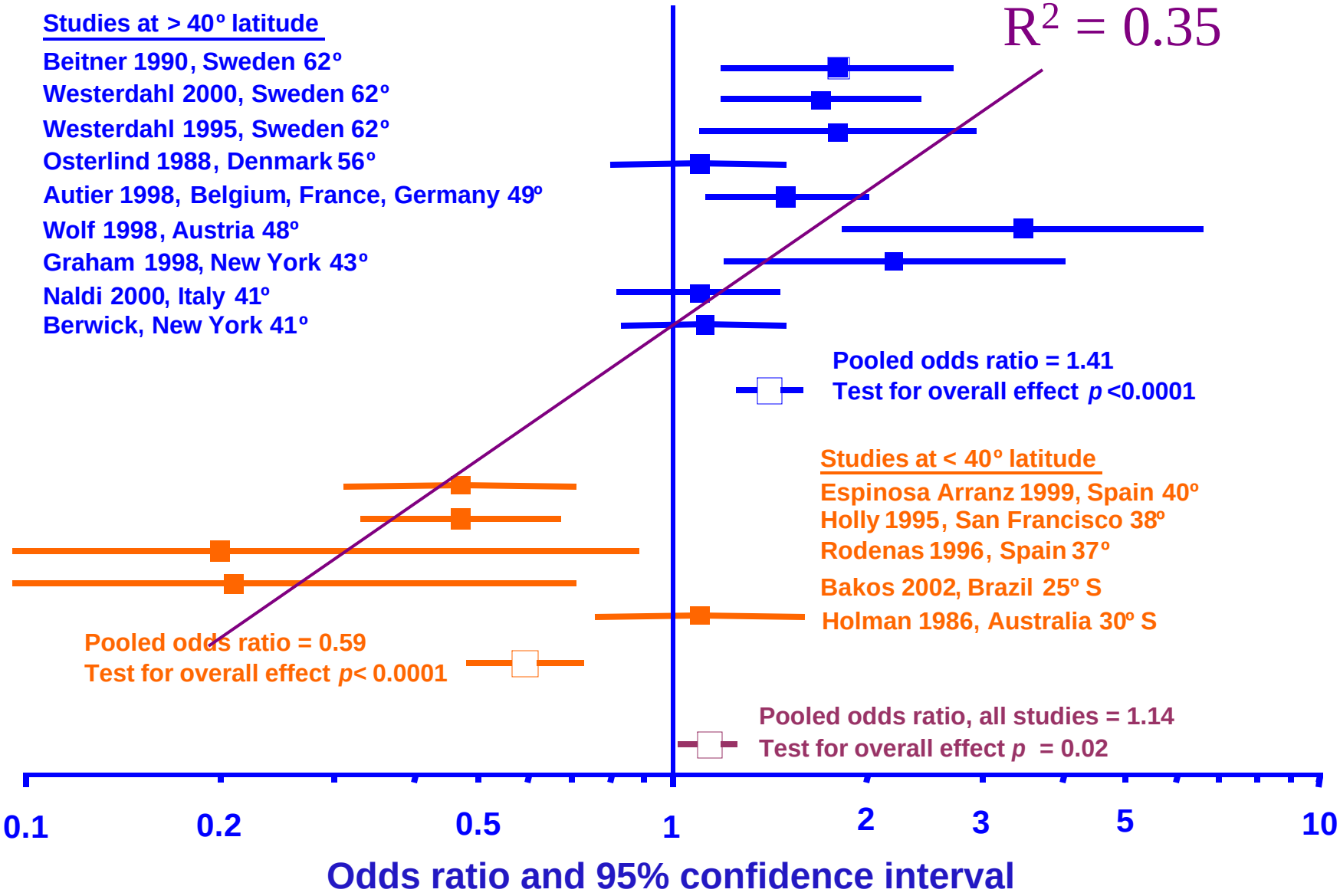
†Source: Jablonski and Chaplin, J Hum Evol 2000; 39:57-106.

16 Case-Control Studies of Sunscreen Use and Melanoma

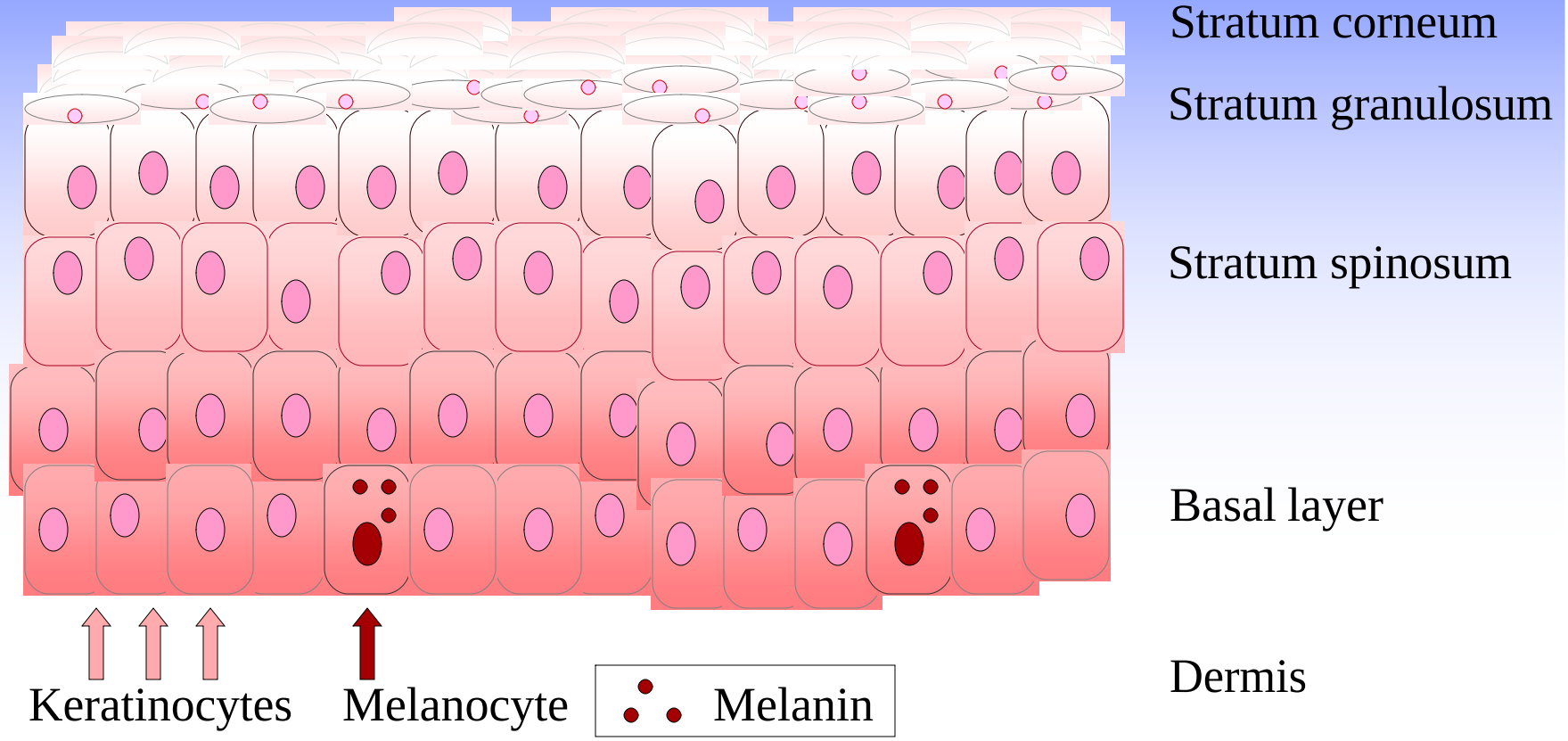


Odds Ratios for malignant melanoma associated with sunscreen use

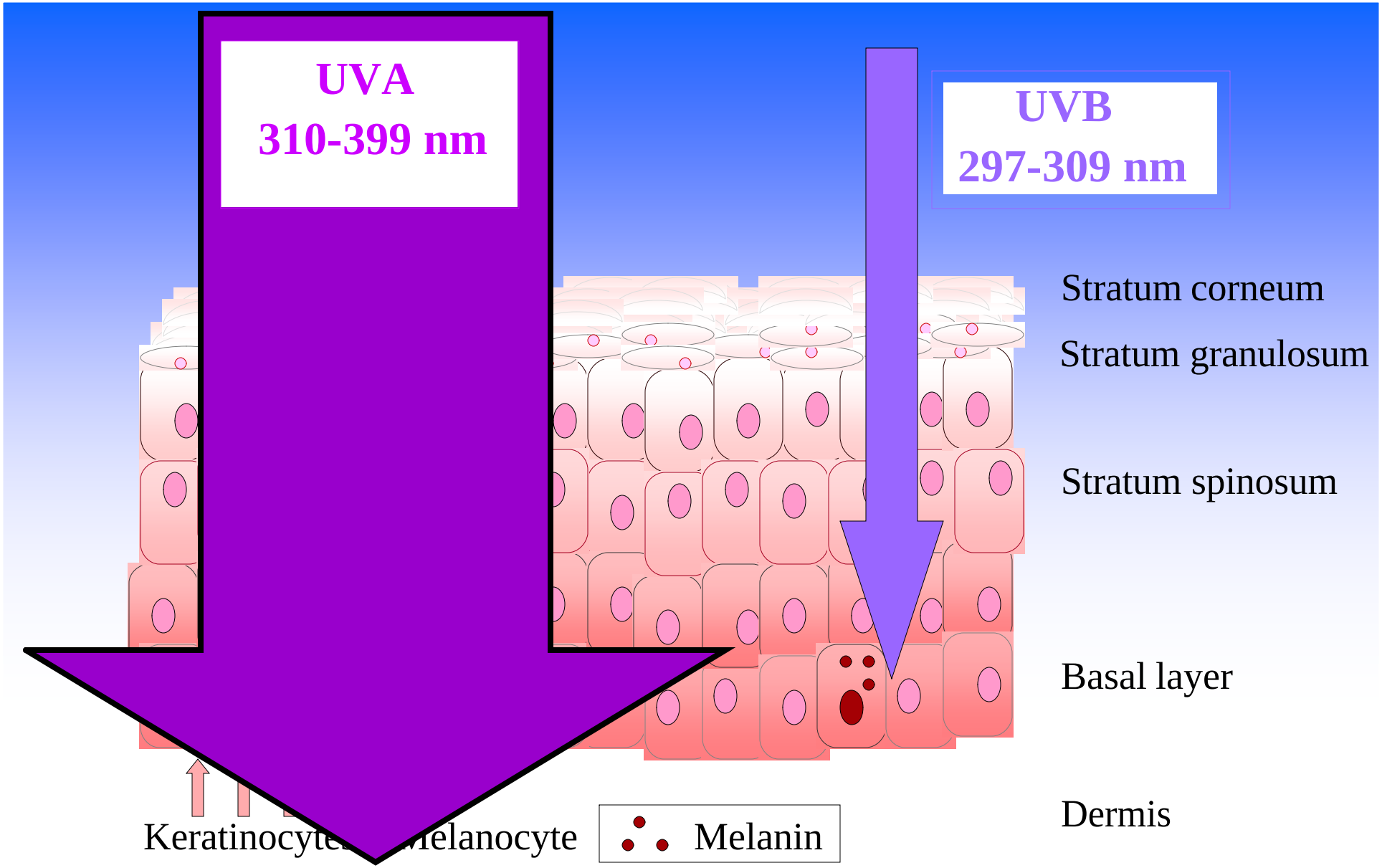
(4 lower, 5 not statistically significant, 7 elevated)



Source: Gorham ED, Mohr SB, Garland CF, Chaplin G, Garland FC. Do sunscreens increase risk of melanoma in populations residing at higher latitudes? Ann Epidemiol. 2007;17:956-63.



Human Photoprotective Response



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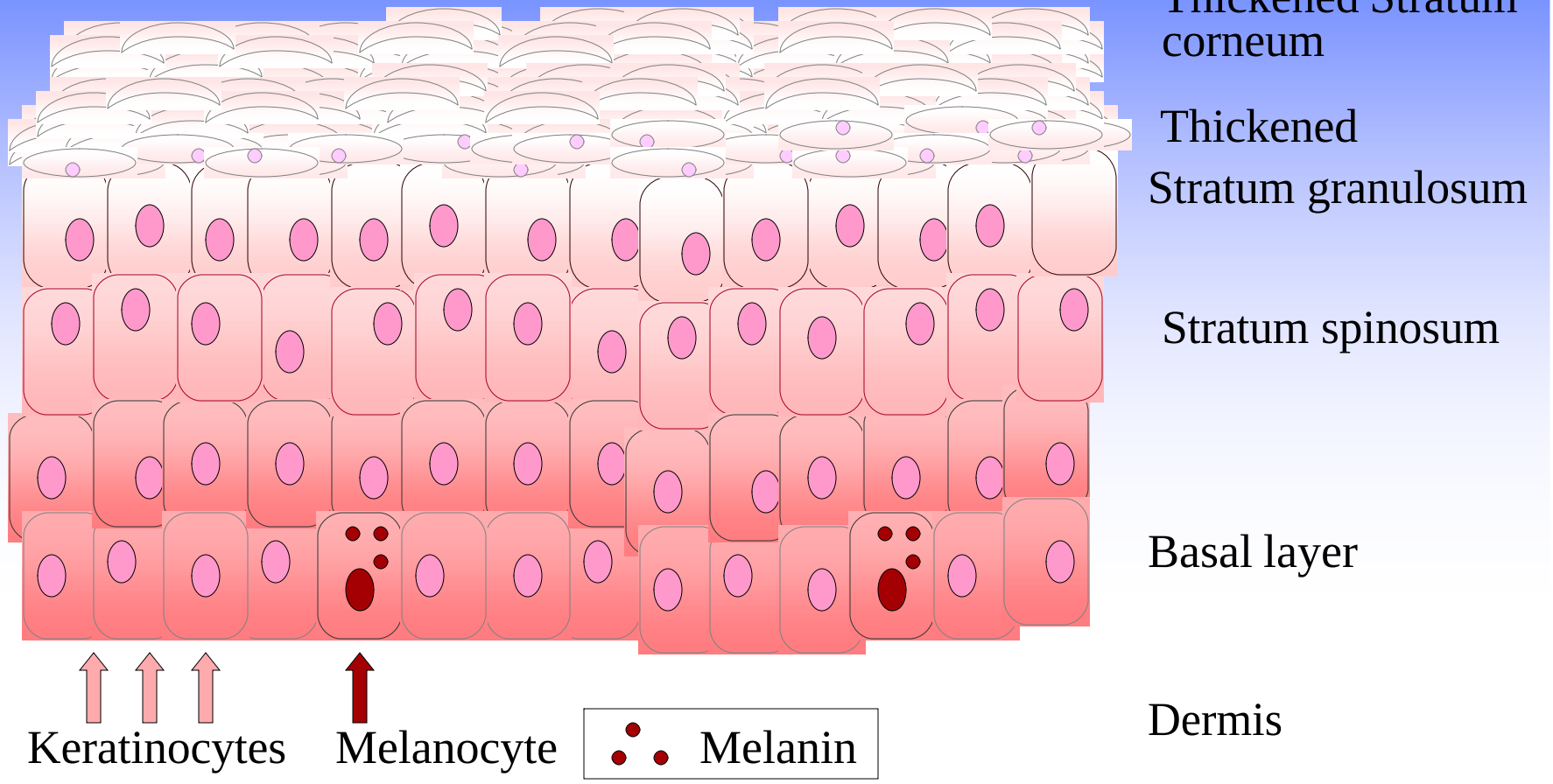

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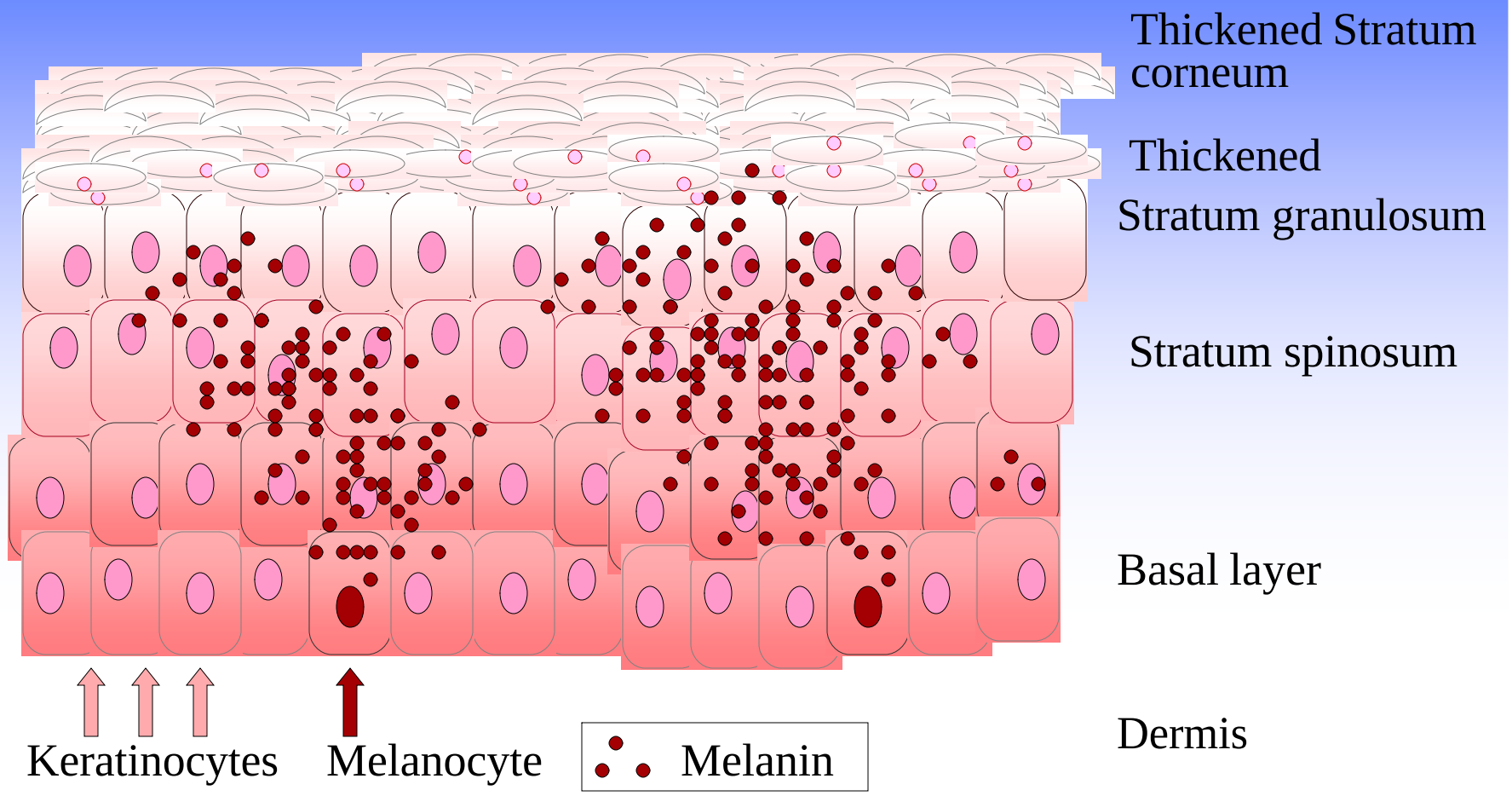

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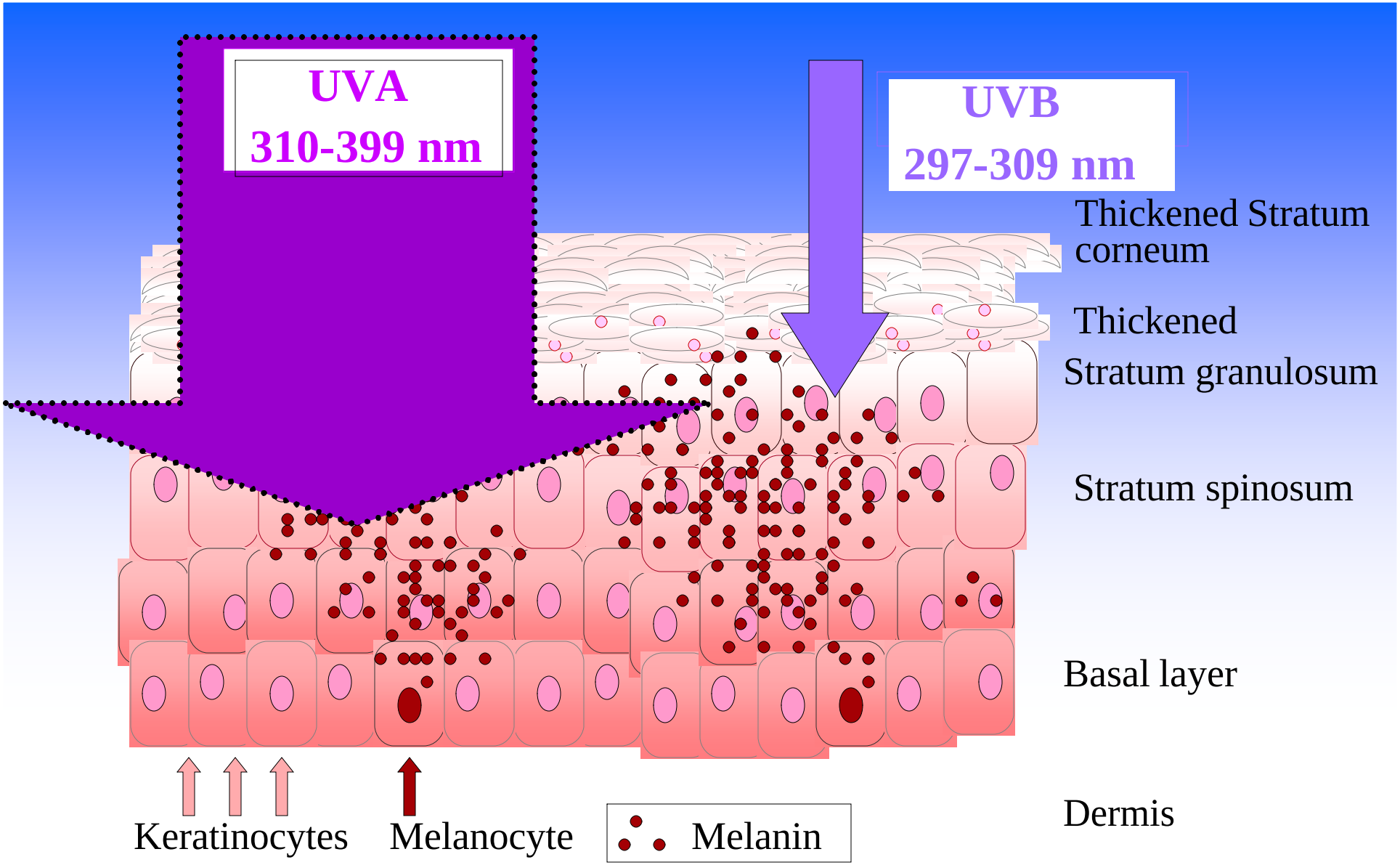

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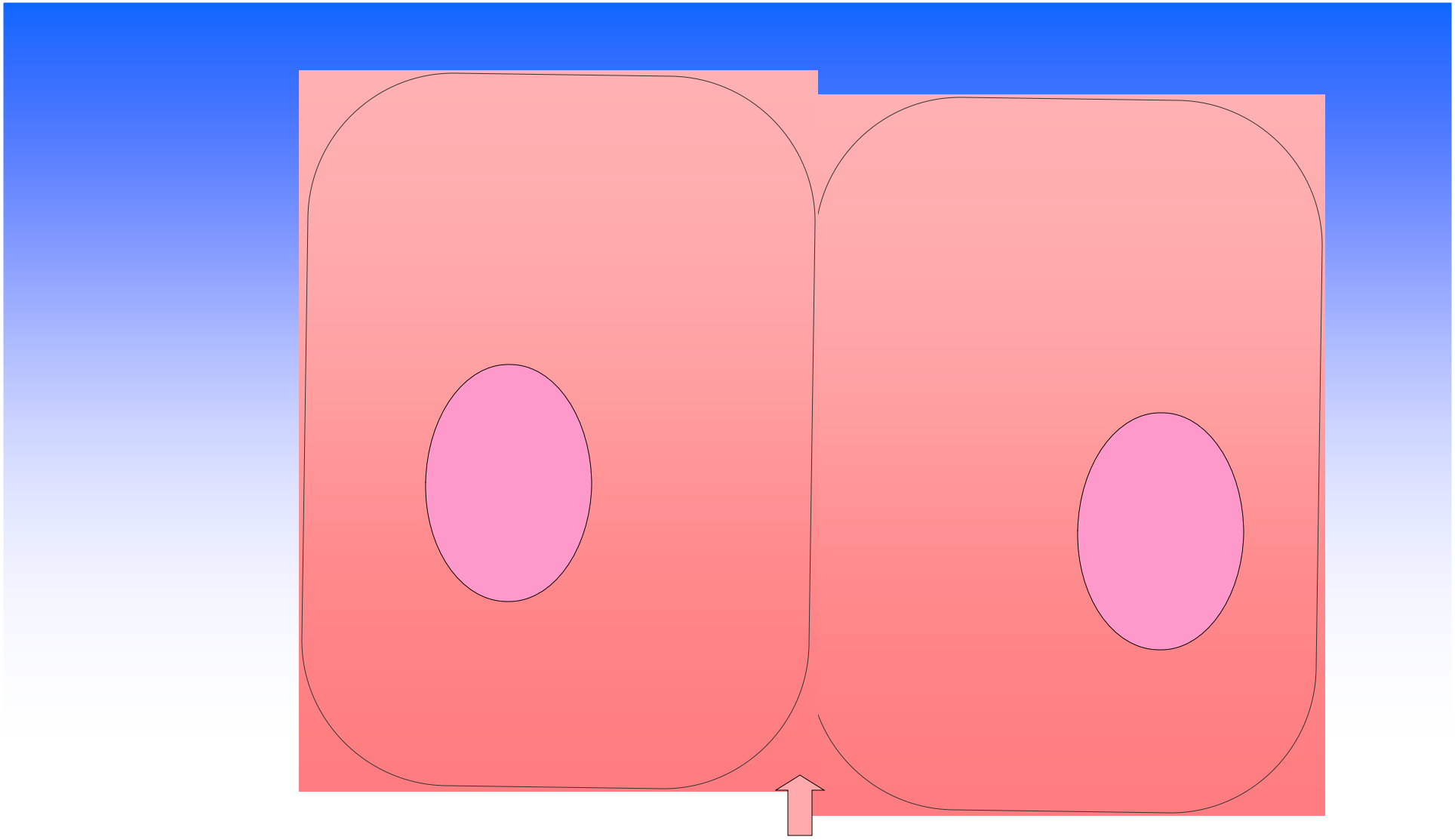
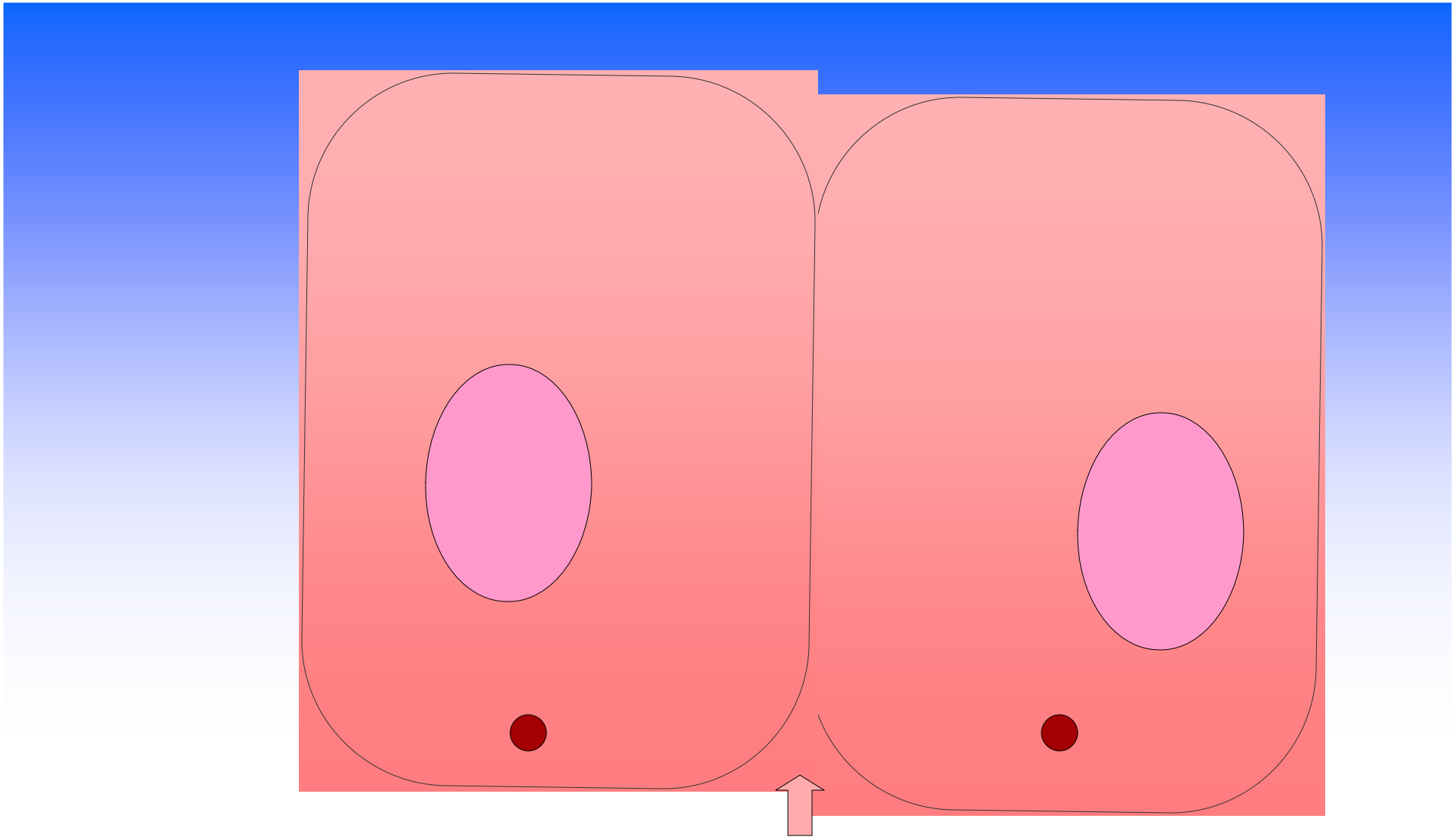


Melanosome migration in response to UV



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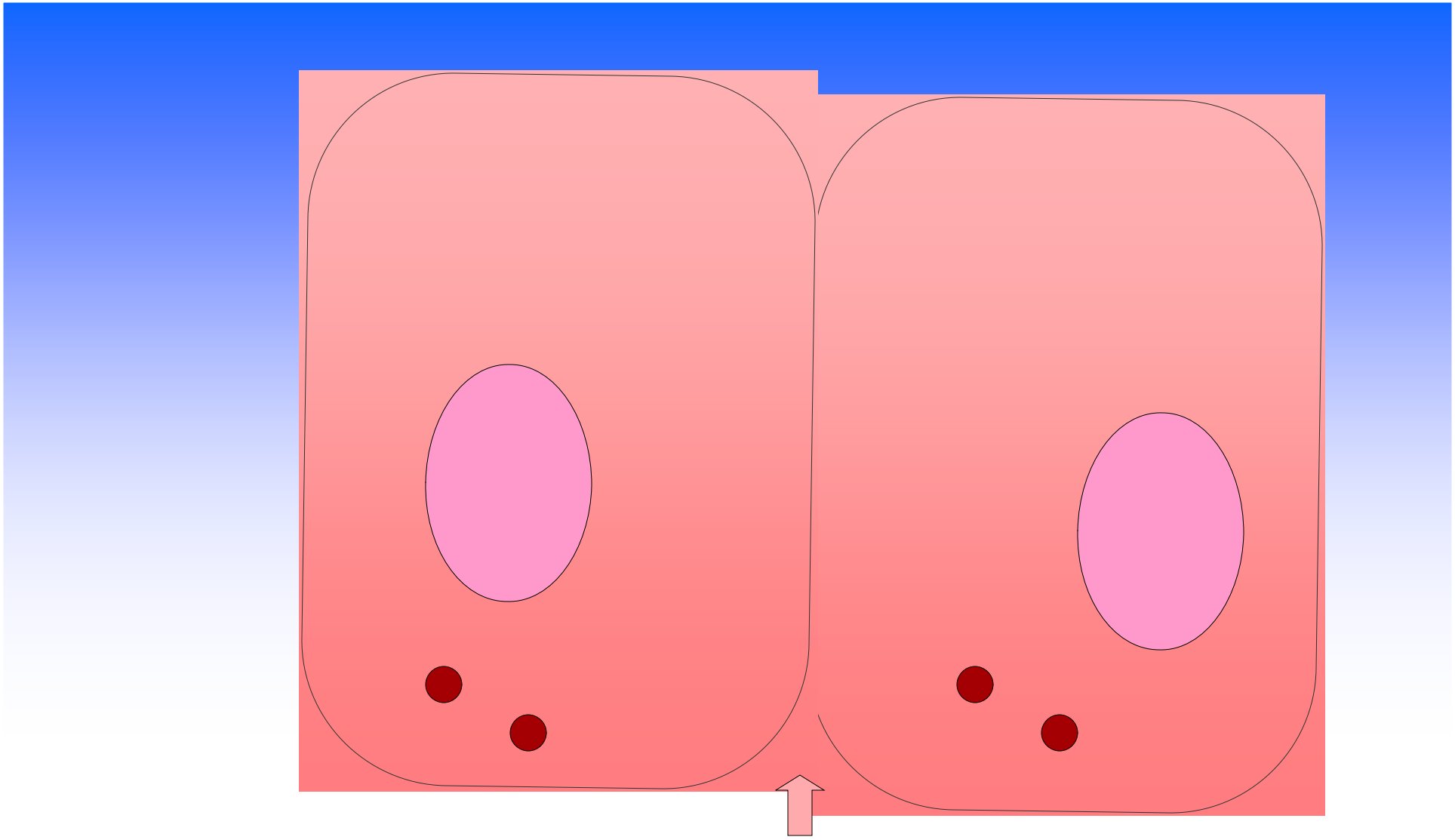

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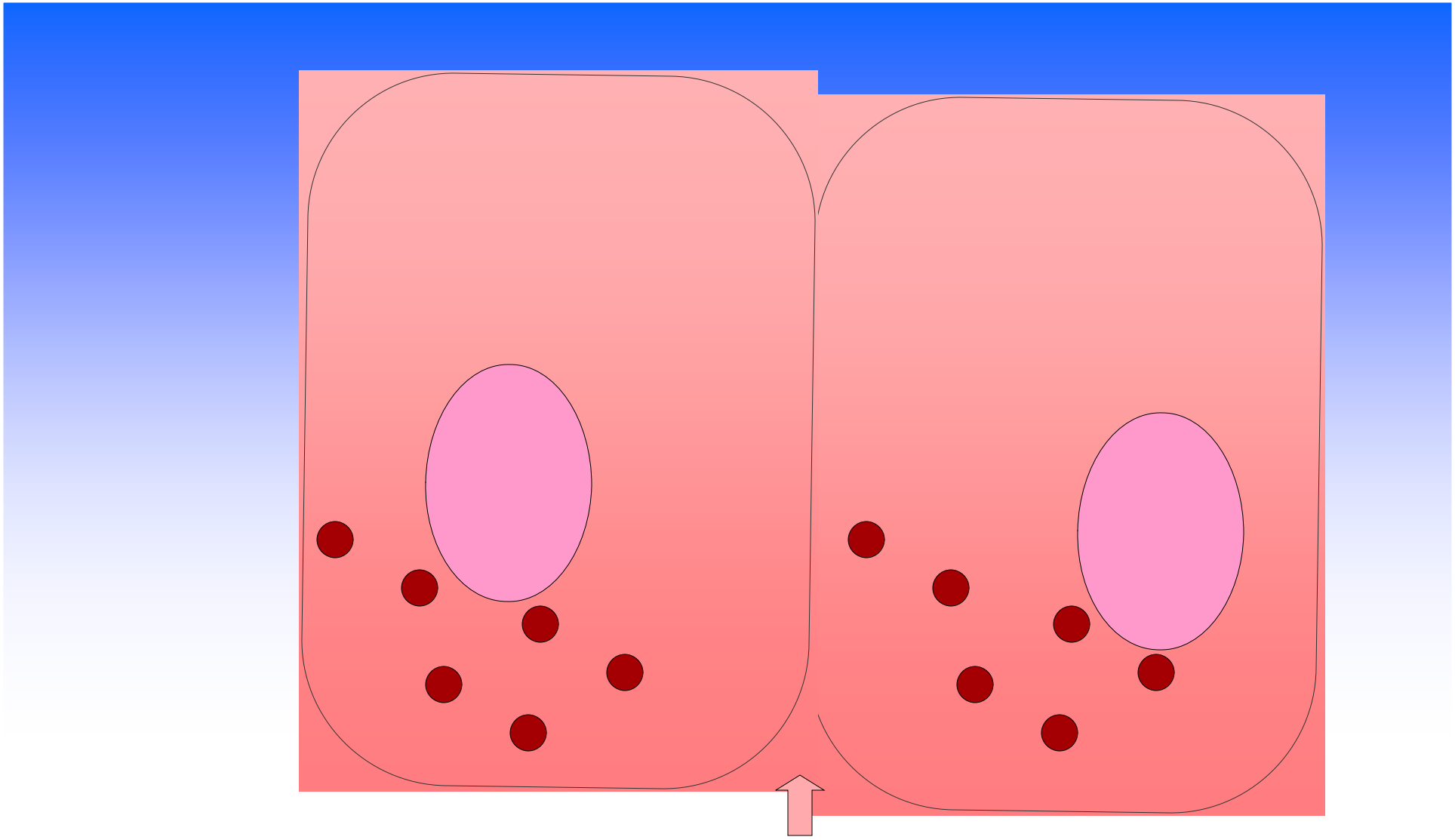

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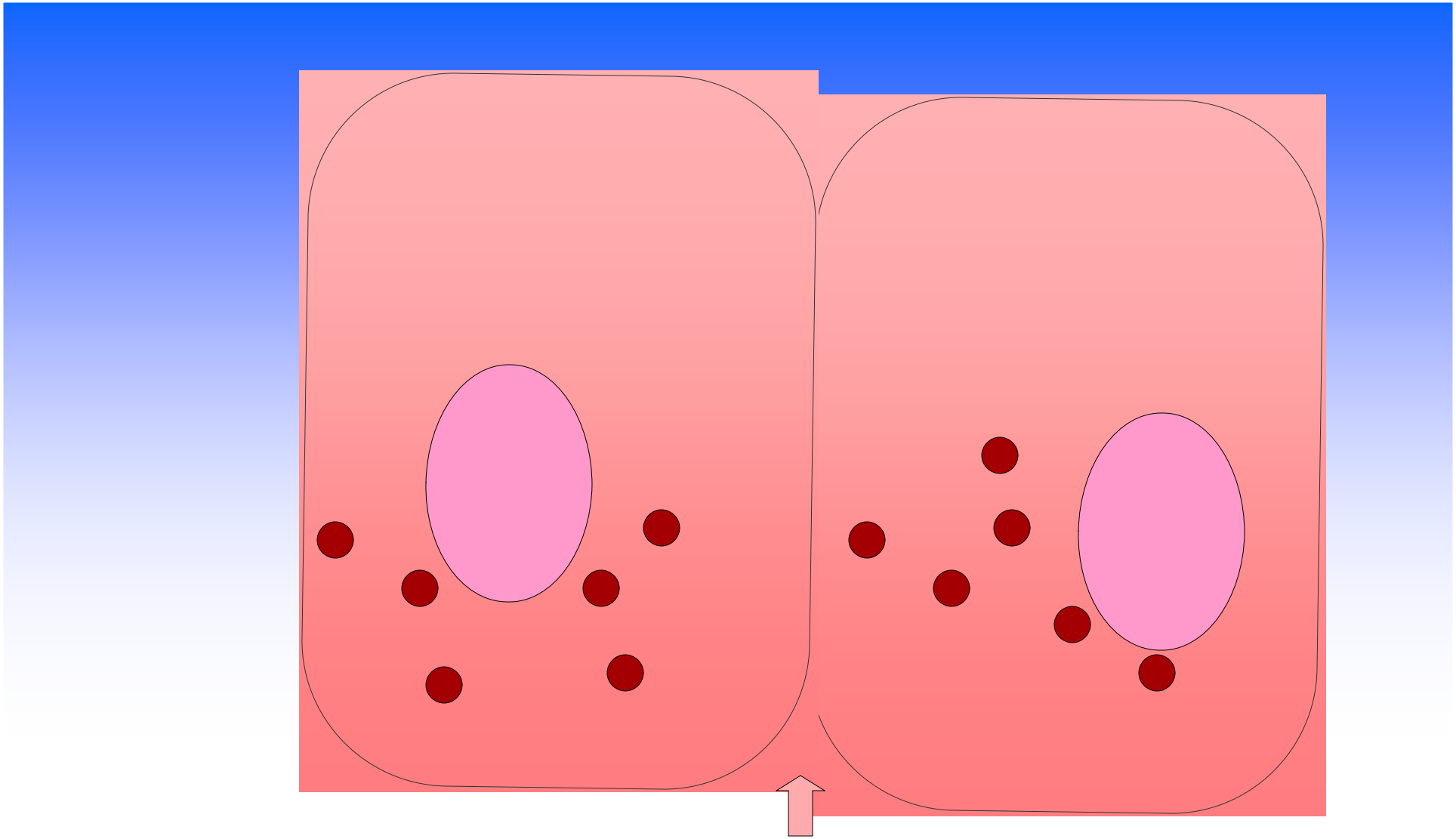

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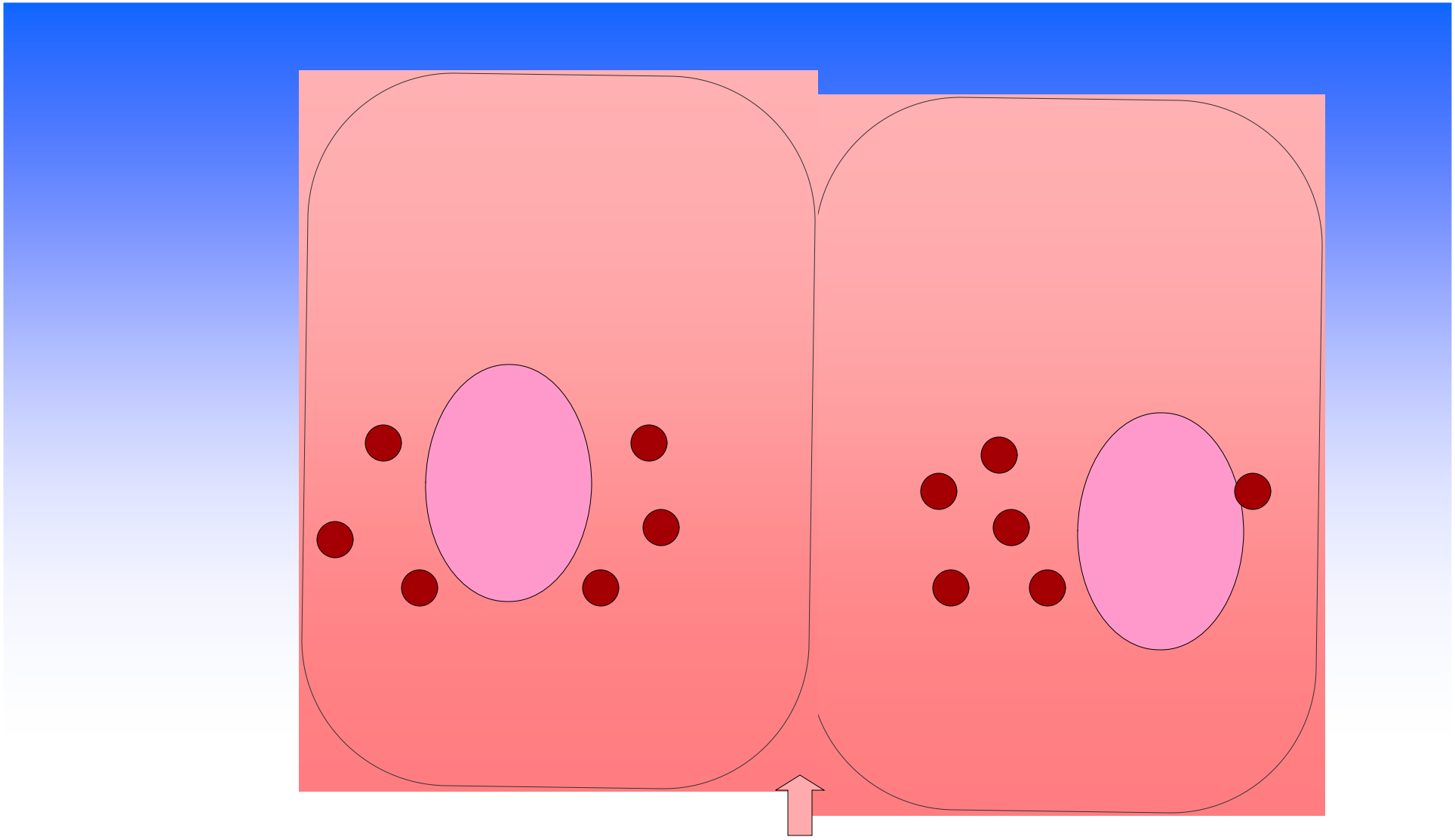

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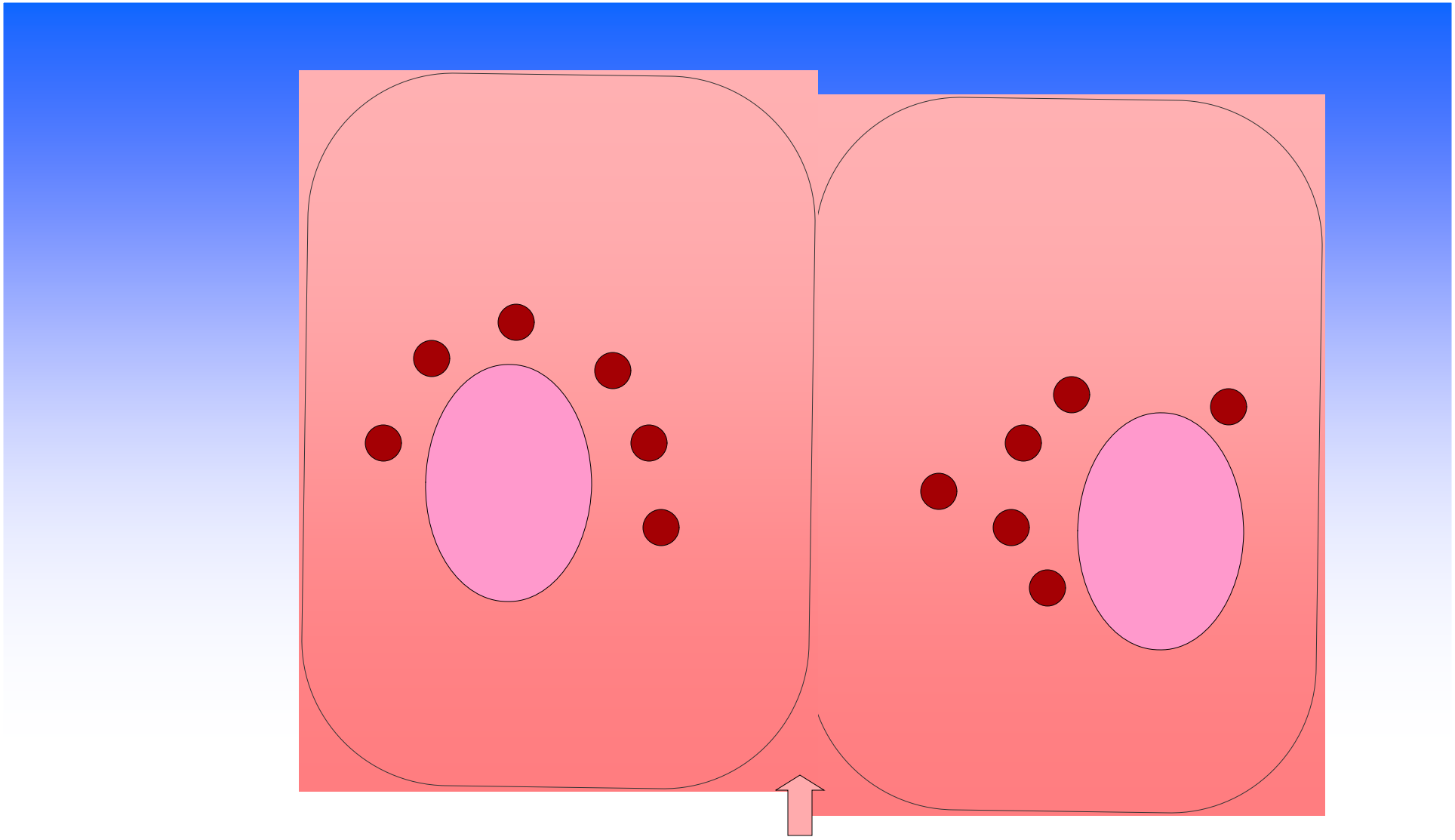

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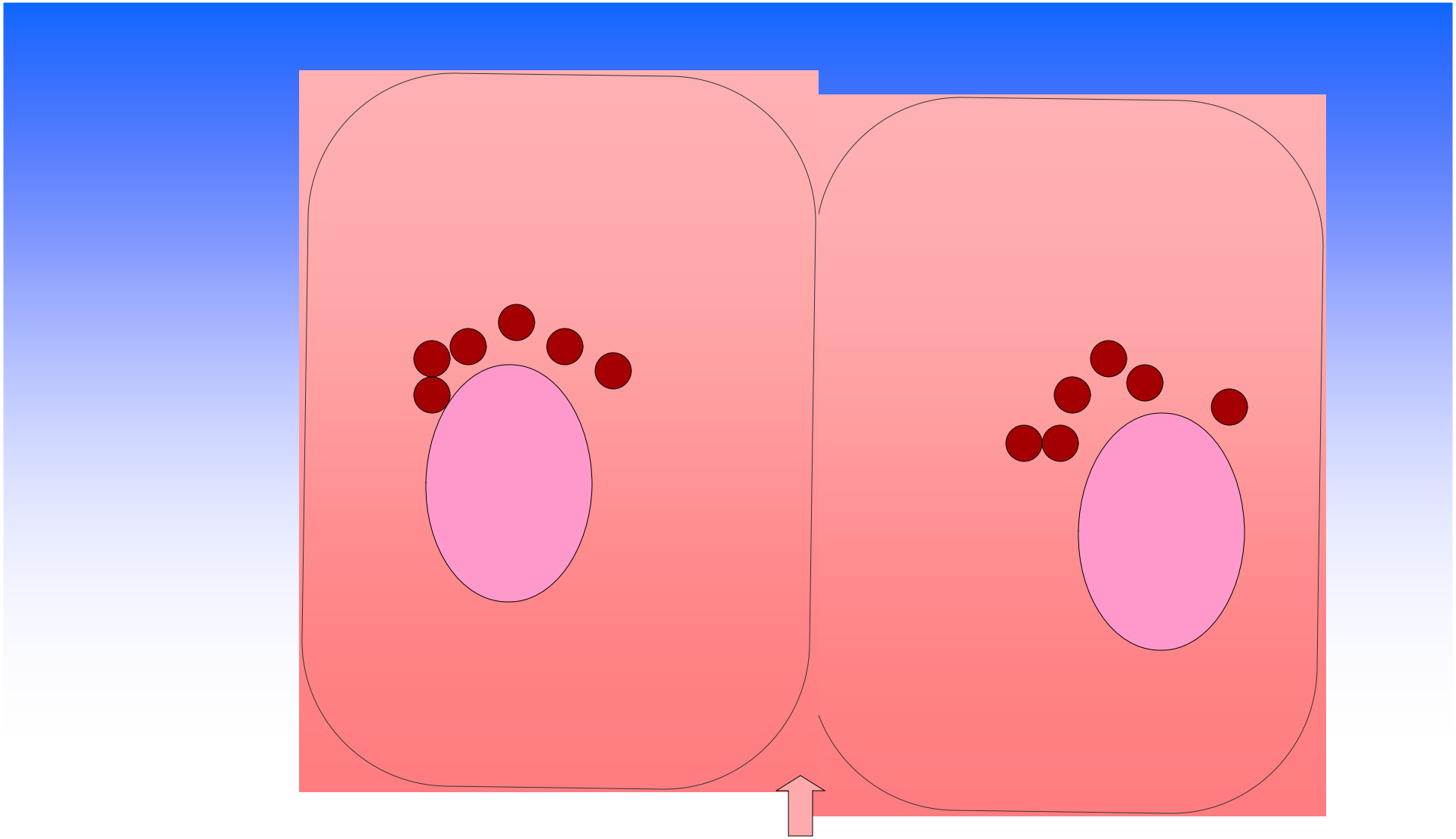
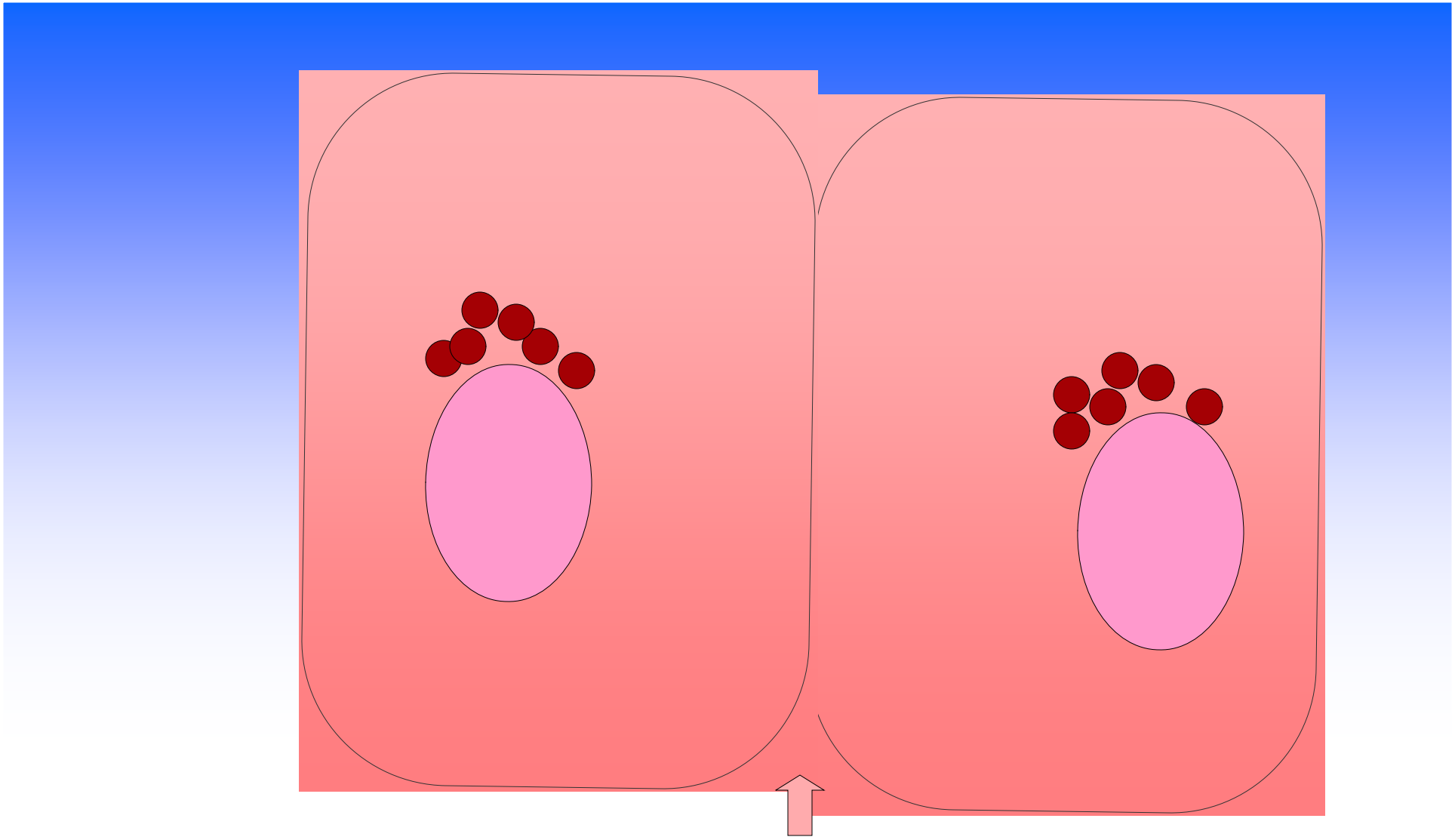


Melanosome migration in response to UV



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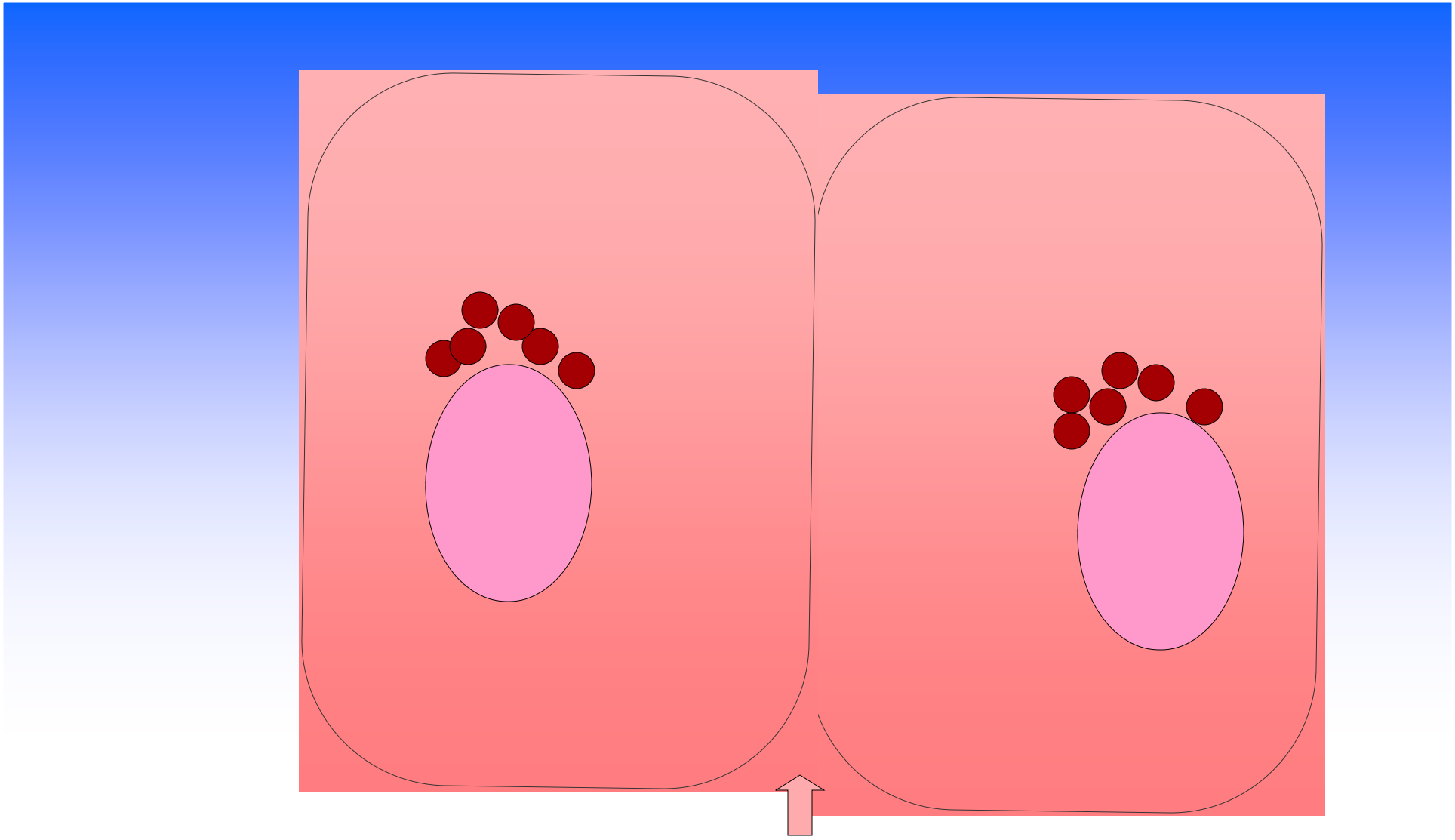

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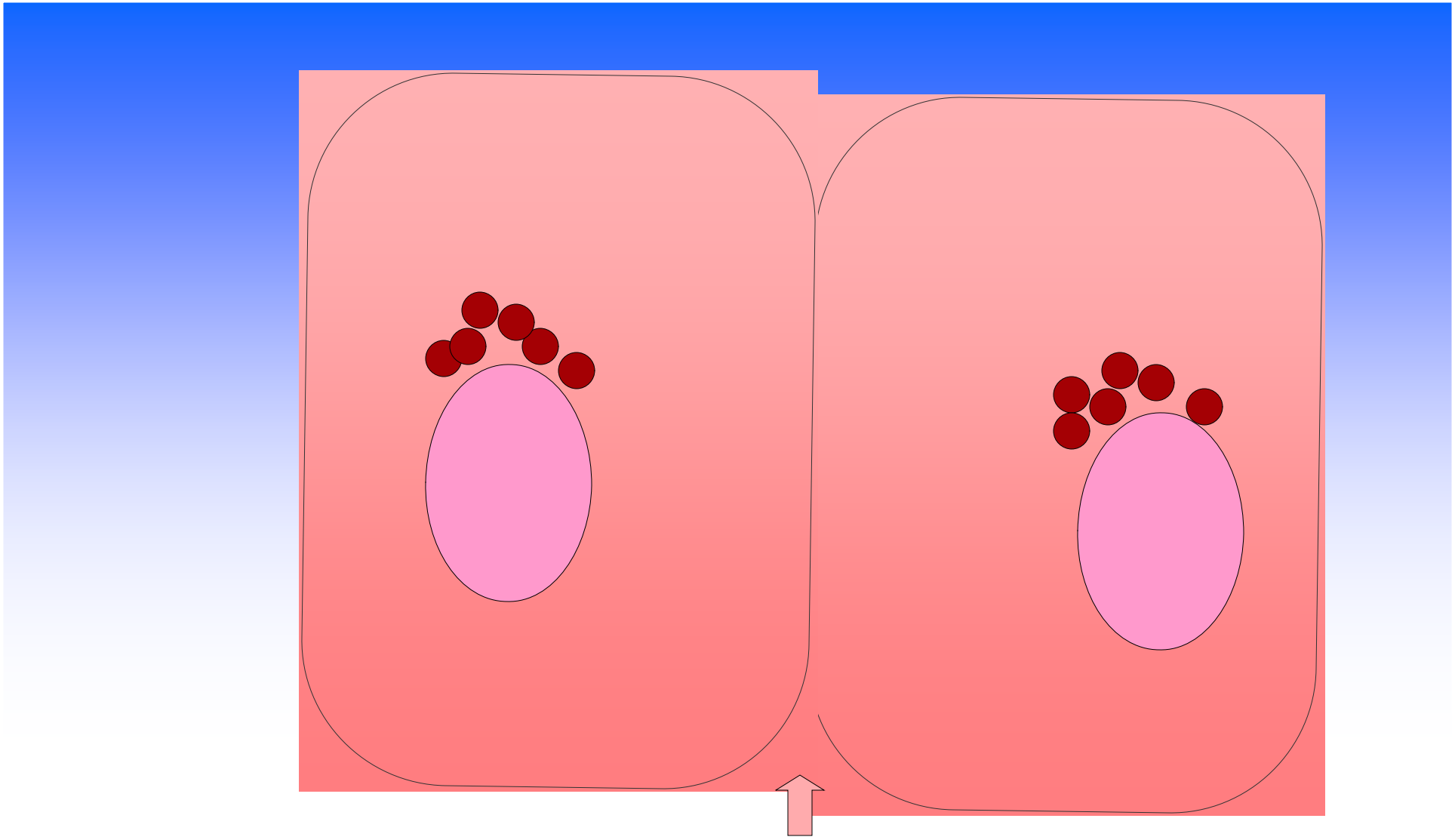
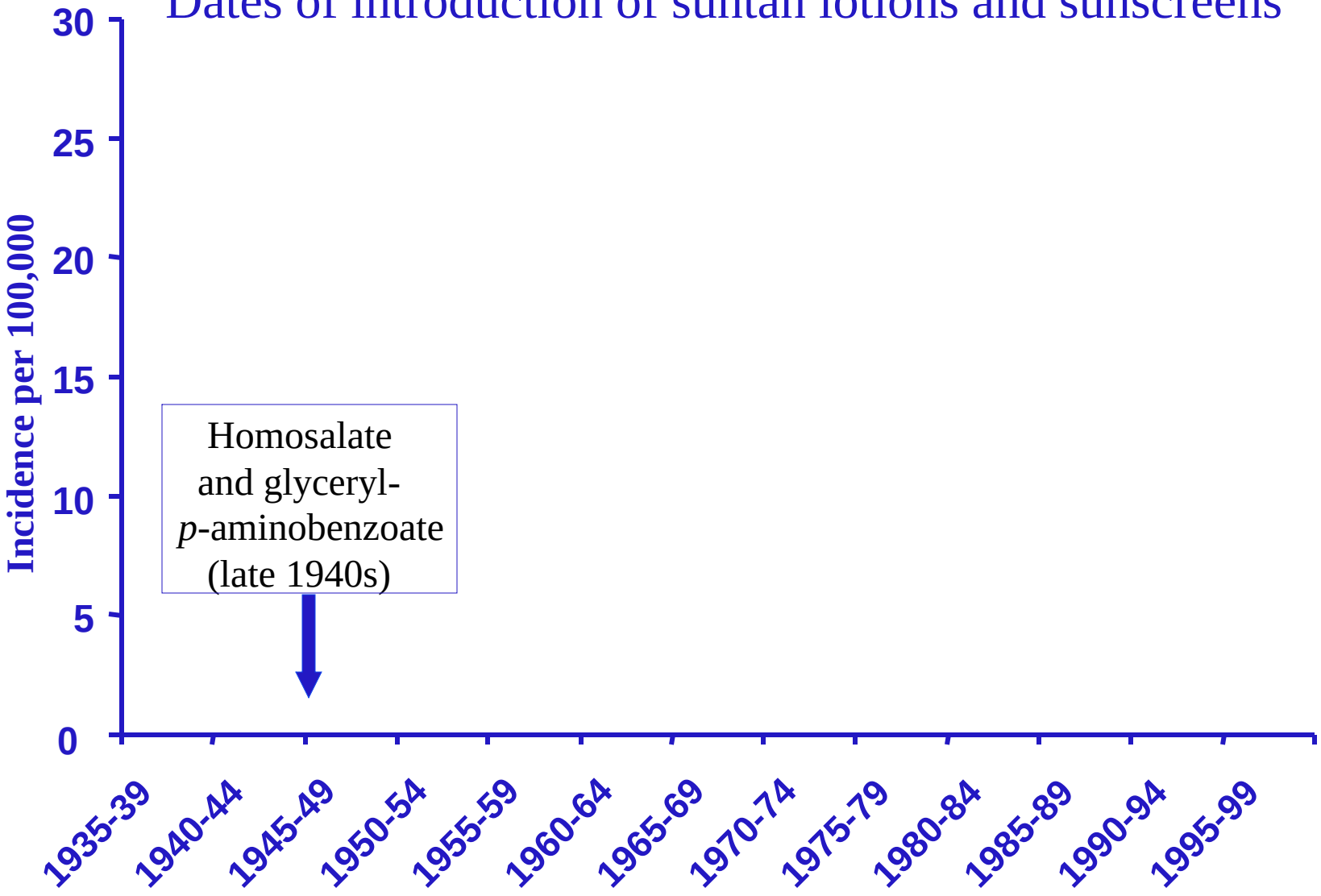


Melanosome migration in response to UV

Dates of introduction of suntan lotions and sunscreens



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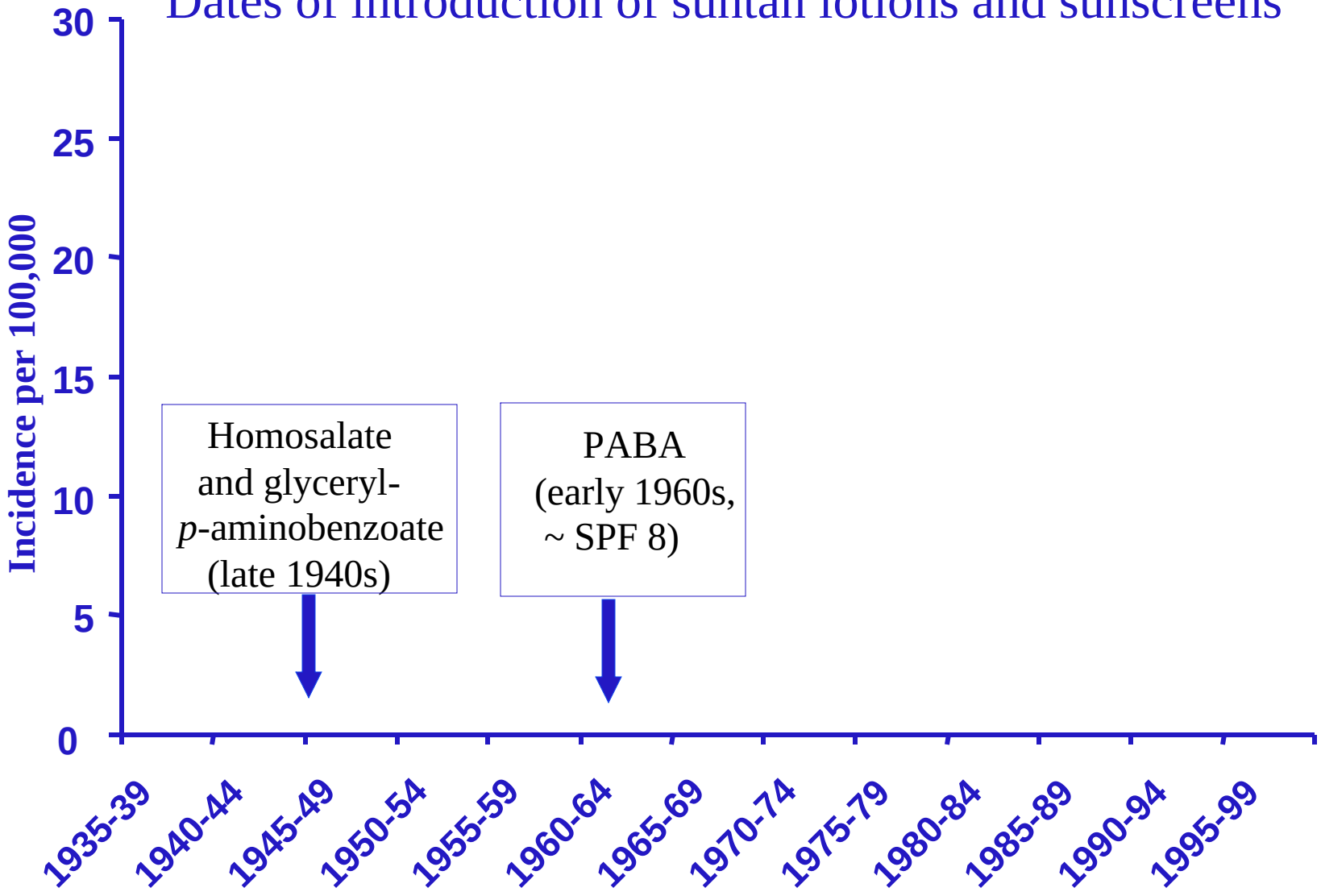

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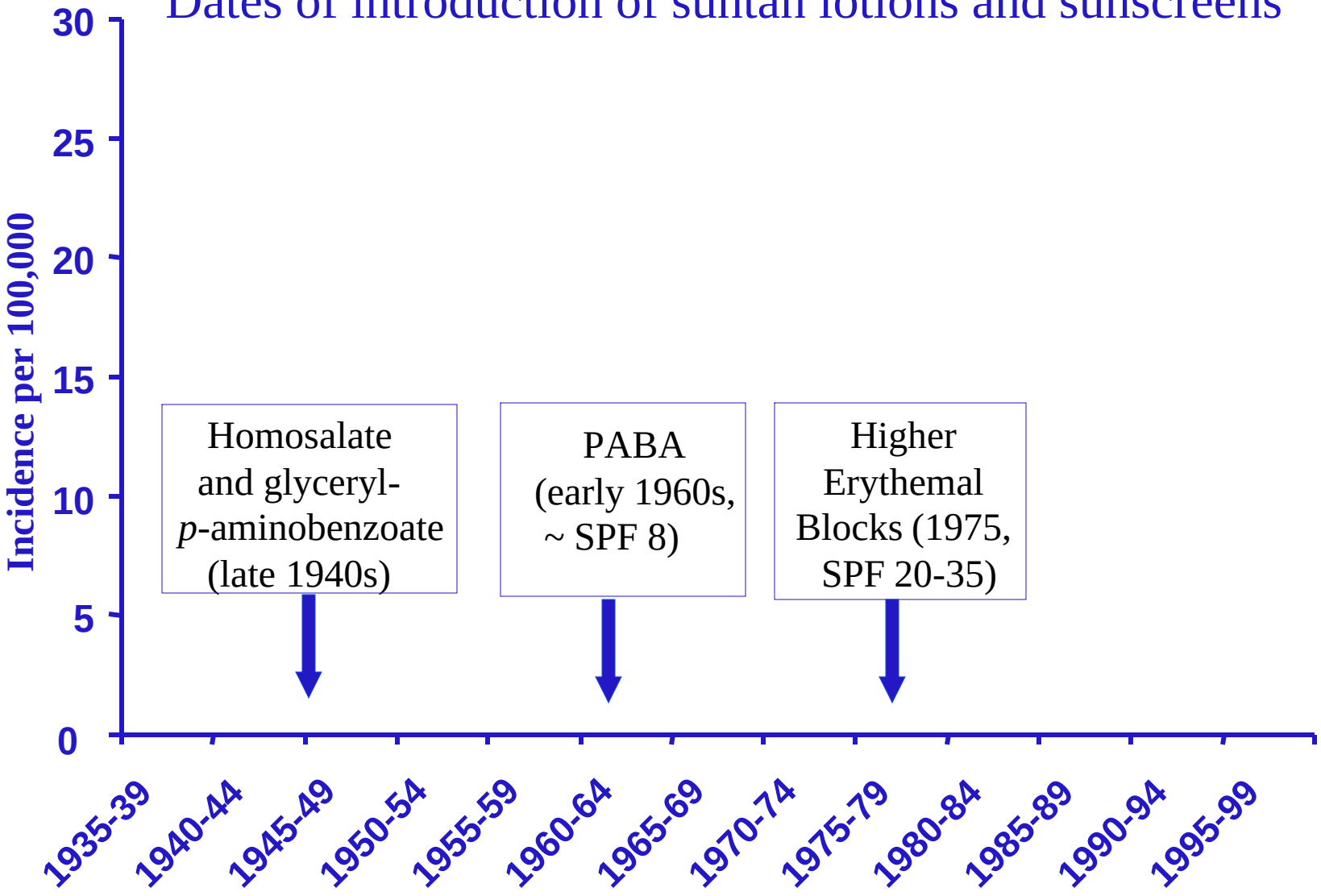
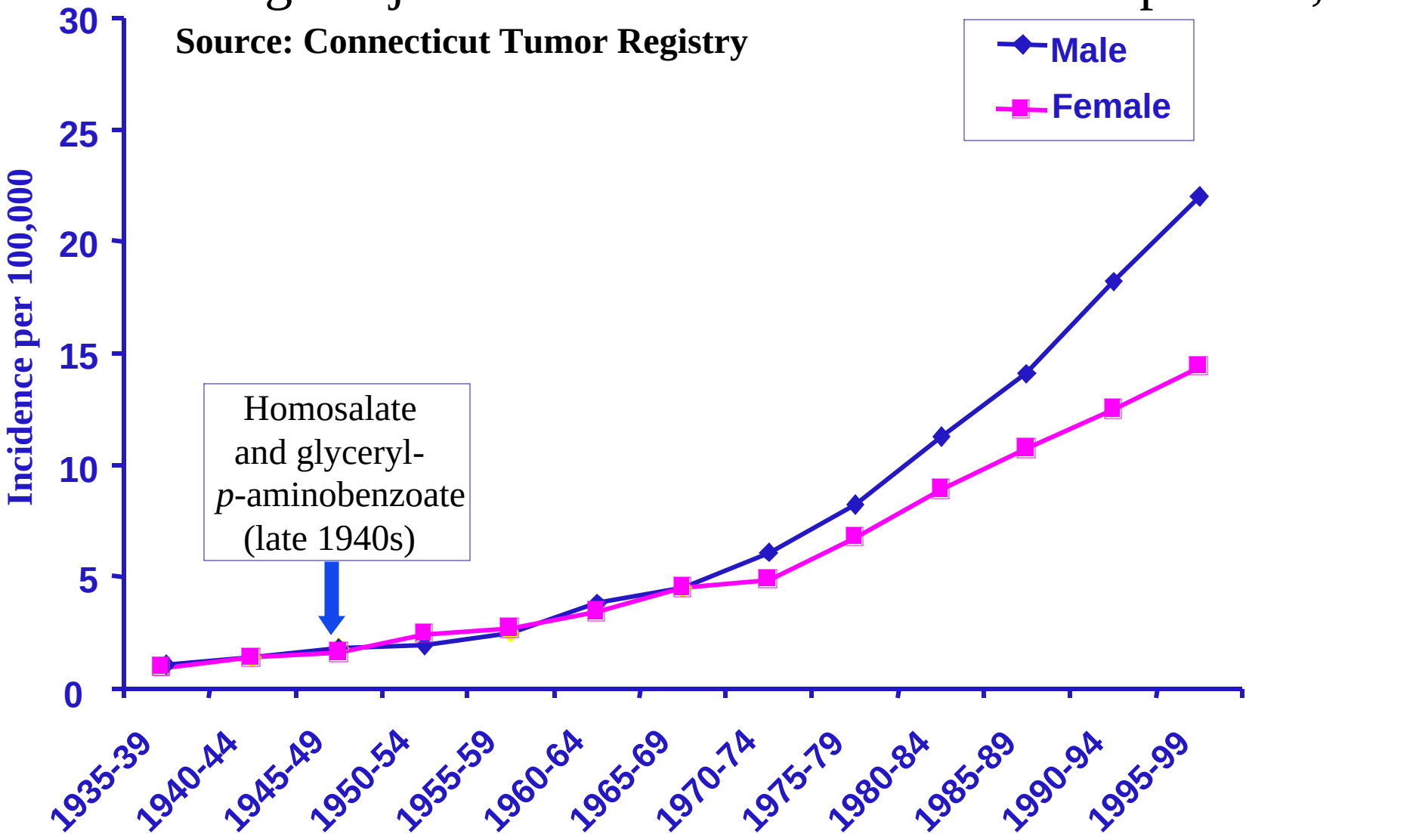


Dates of introduction of suntan lotions and sunscreens and age-adjusted melanoma incidence rates per 100,000



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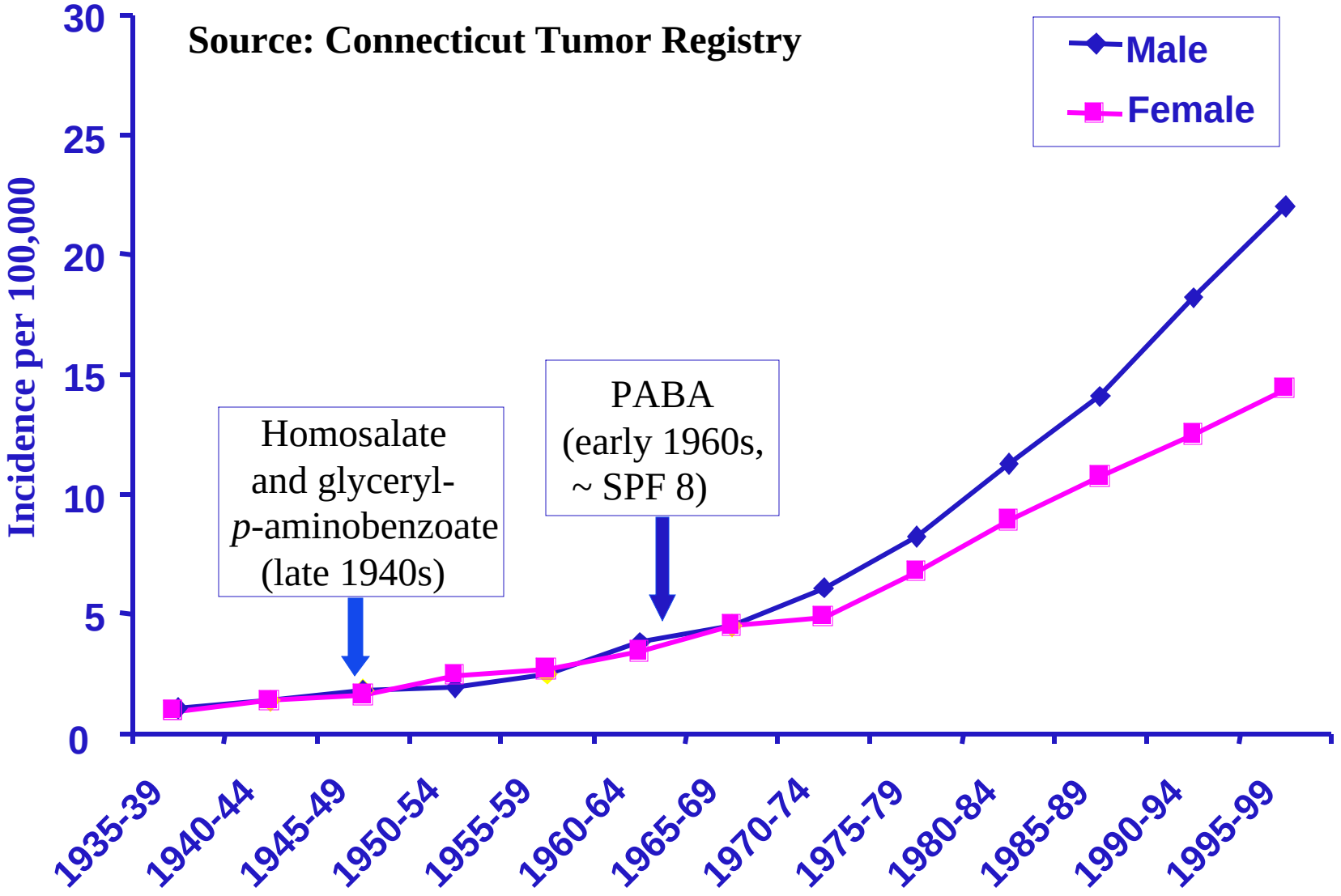

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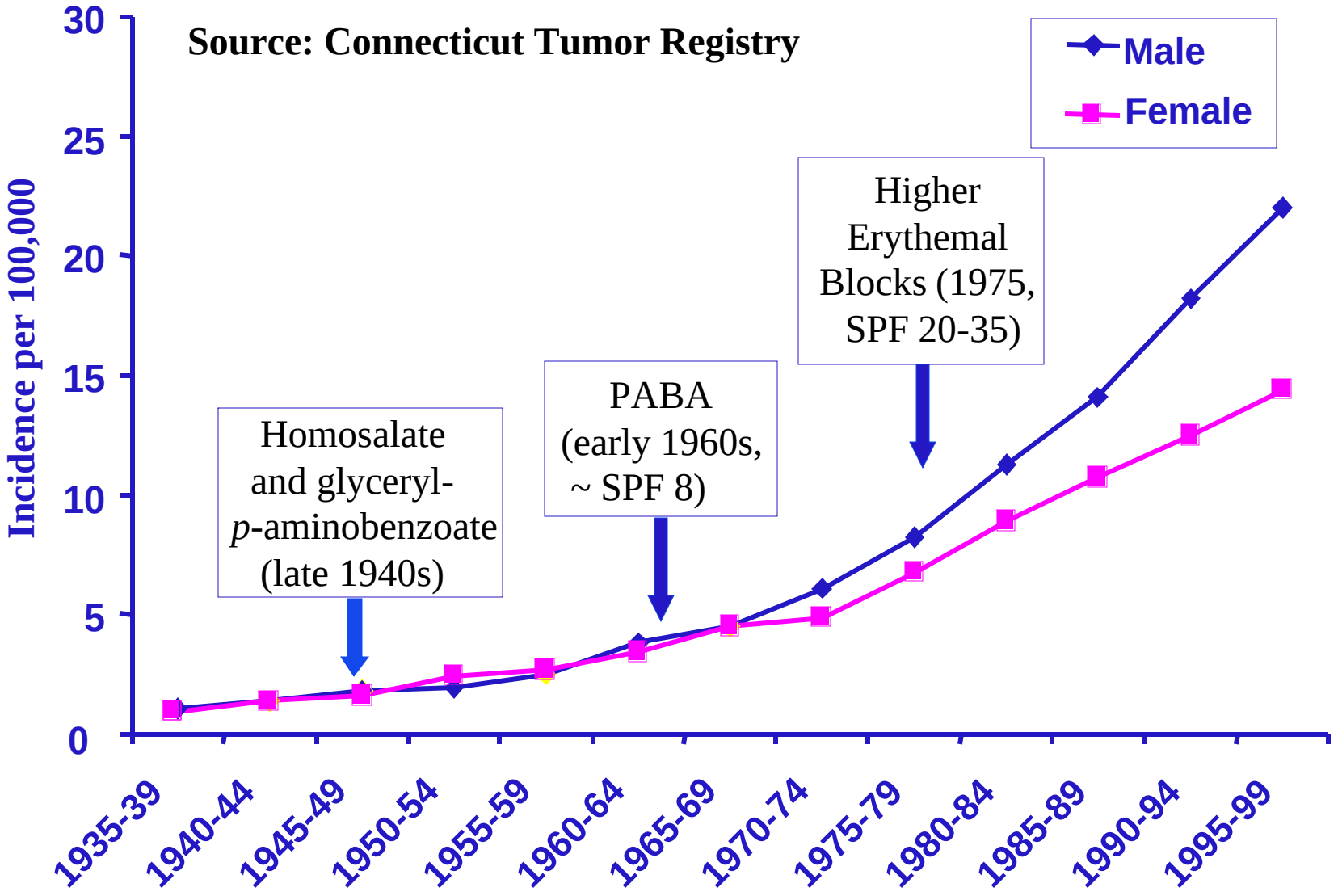

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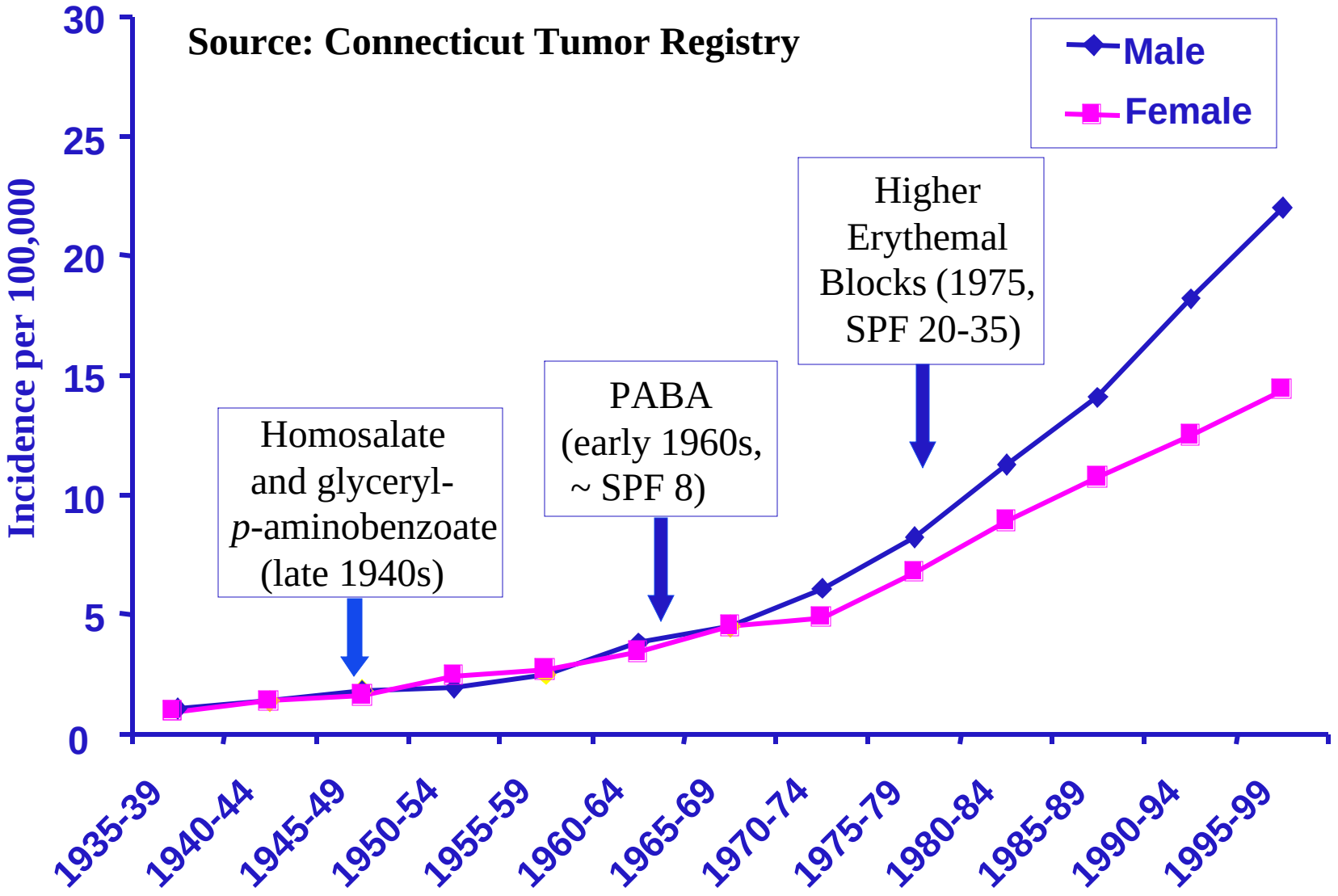
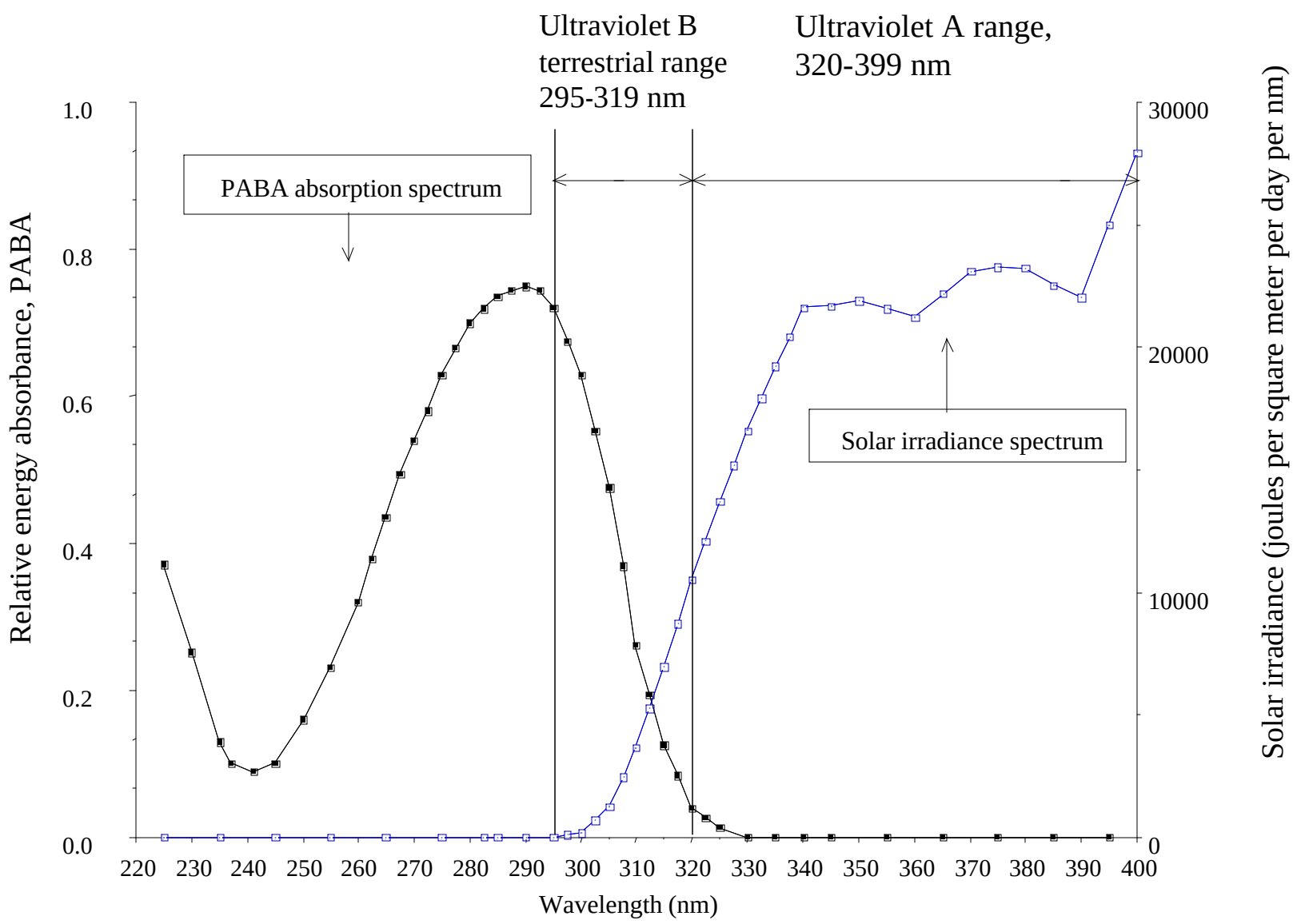
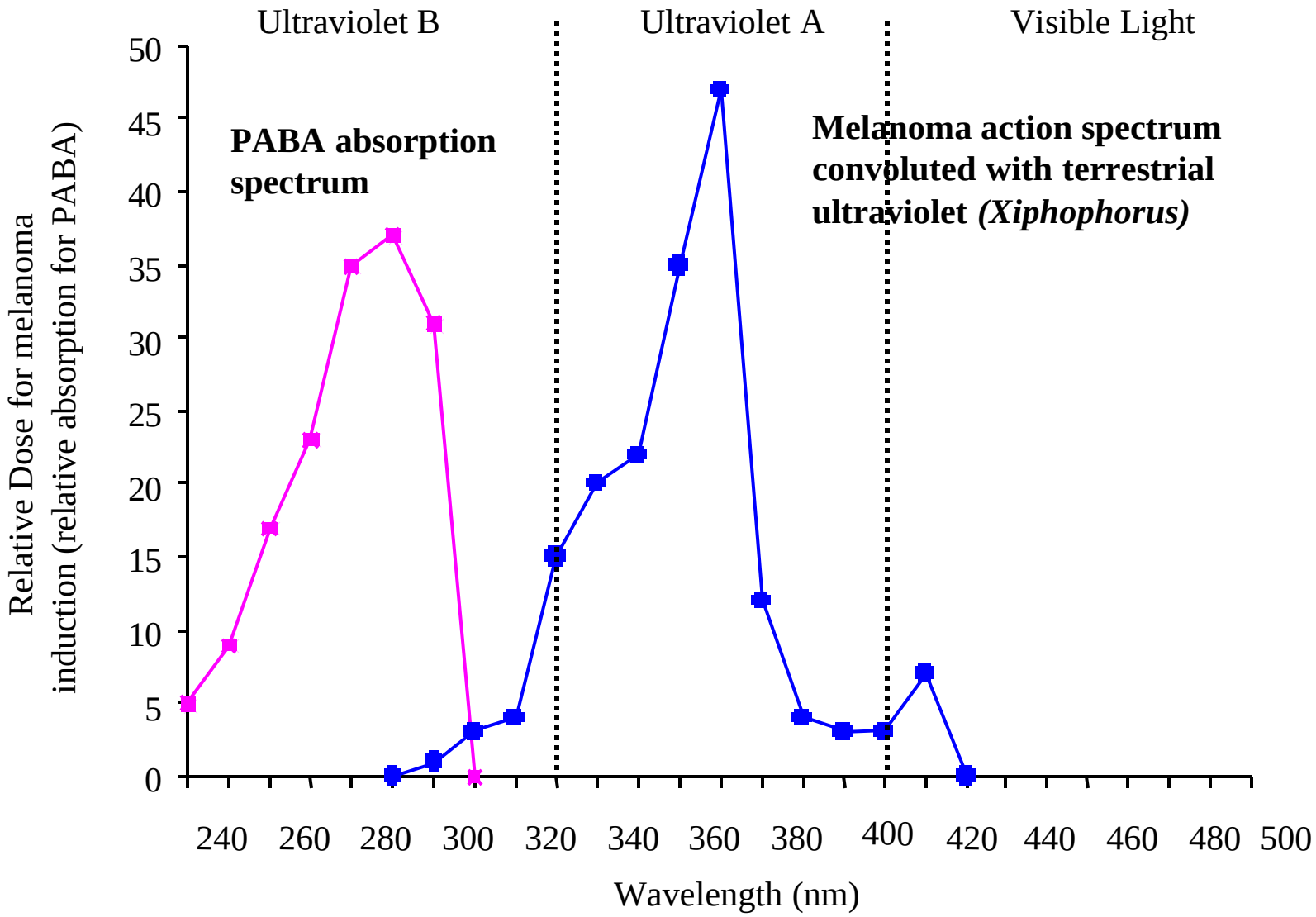


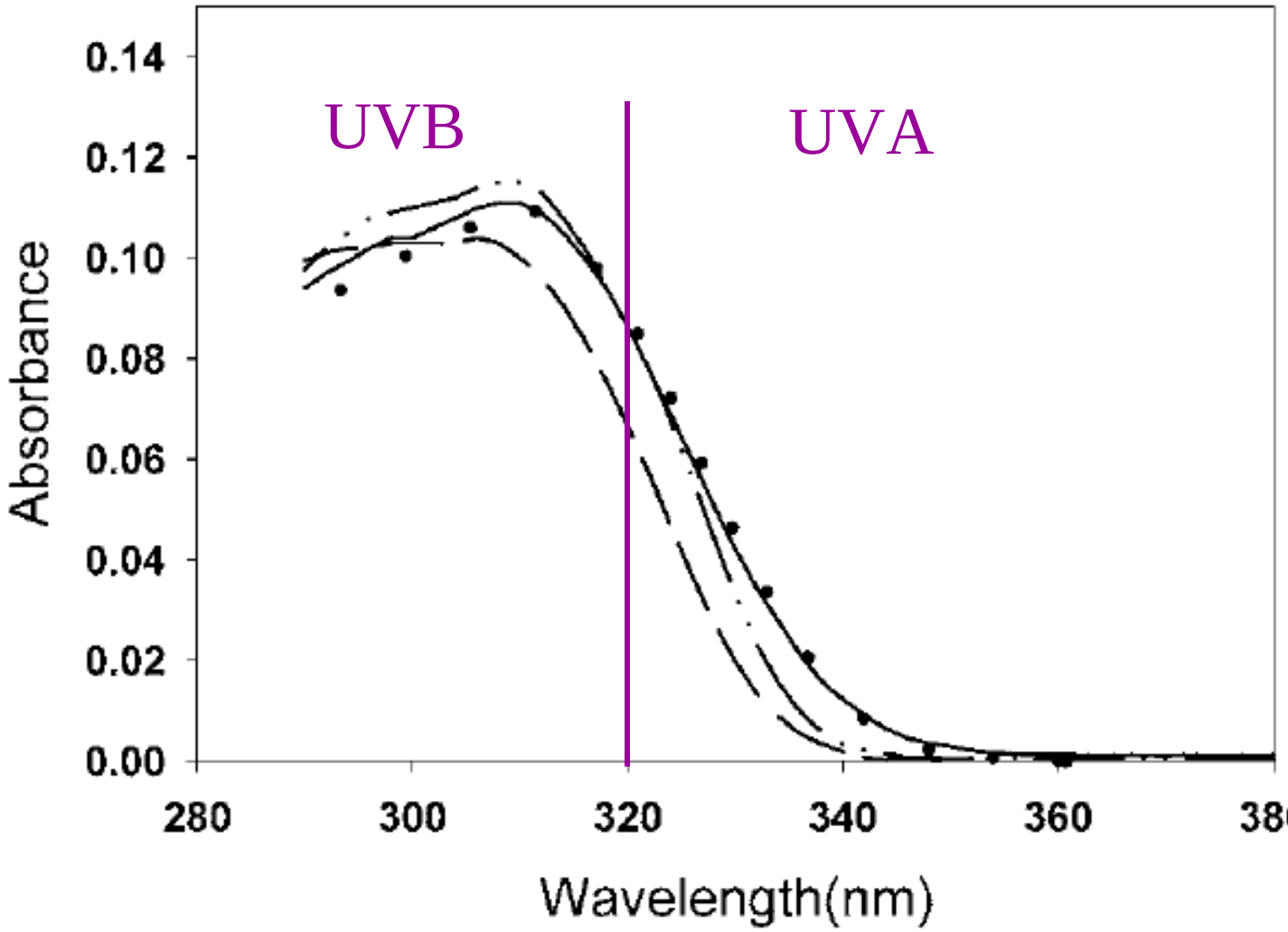


Solar ultraviolet irradiance and relative energy absorbance by para-aminobenzoic acid



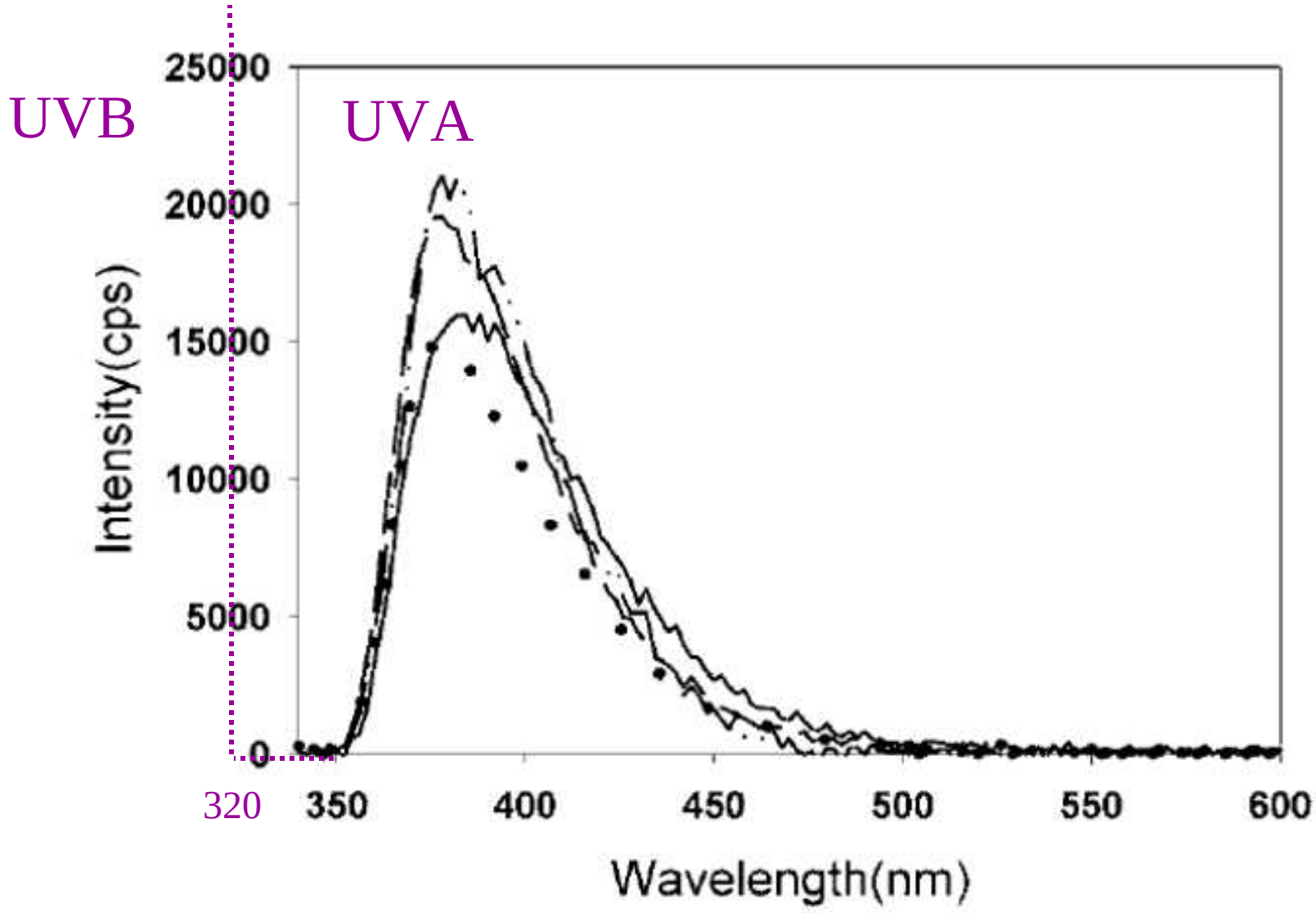
Relative absorption spectrum of PABA sunscreen agent and fish melanoma action spectrum

Source: Setlow RB, Woodhead AD. Temporal Changes in the incidence of melanoma: explanation from an action spectrum. Mutation Res 1994; 307: 365-74.



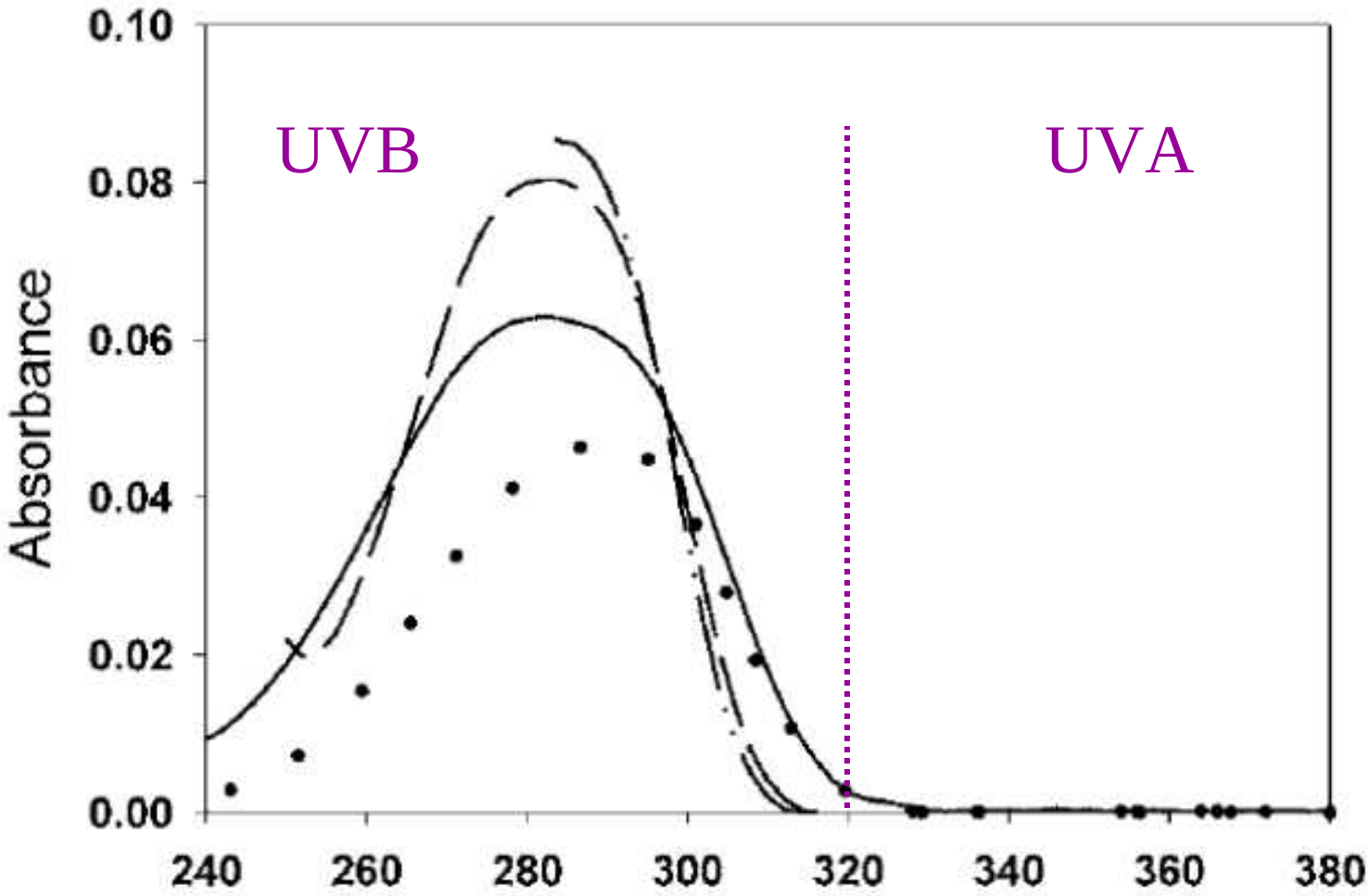
Absorption spectrum of octyl methoxycinnamate
in toulene (— --); ethyl acetate (– –); 1 propanol (---); and methanol (—)

Source: Krishnan R, Carr A, Blair E, Nordlund TM. Optical spectroscopy of hydrophobic sunscreen molecules adsorbed to dielectric nanospheres.Photochem Photobiol. 2004 Jun;79(6):531-9



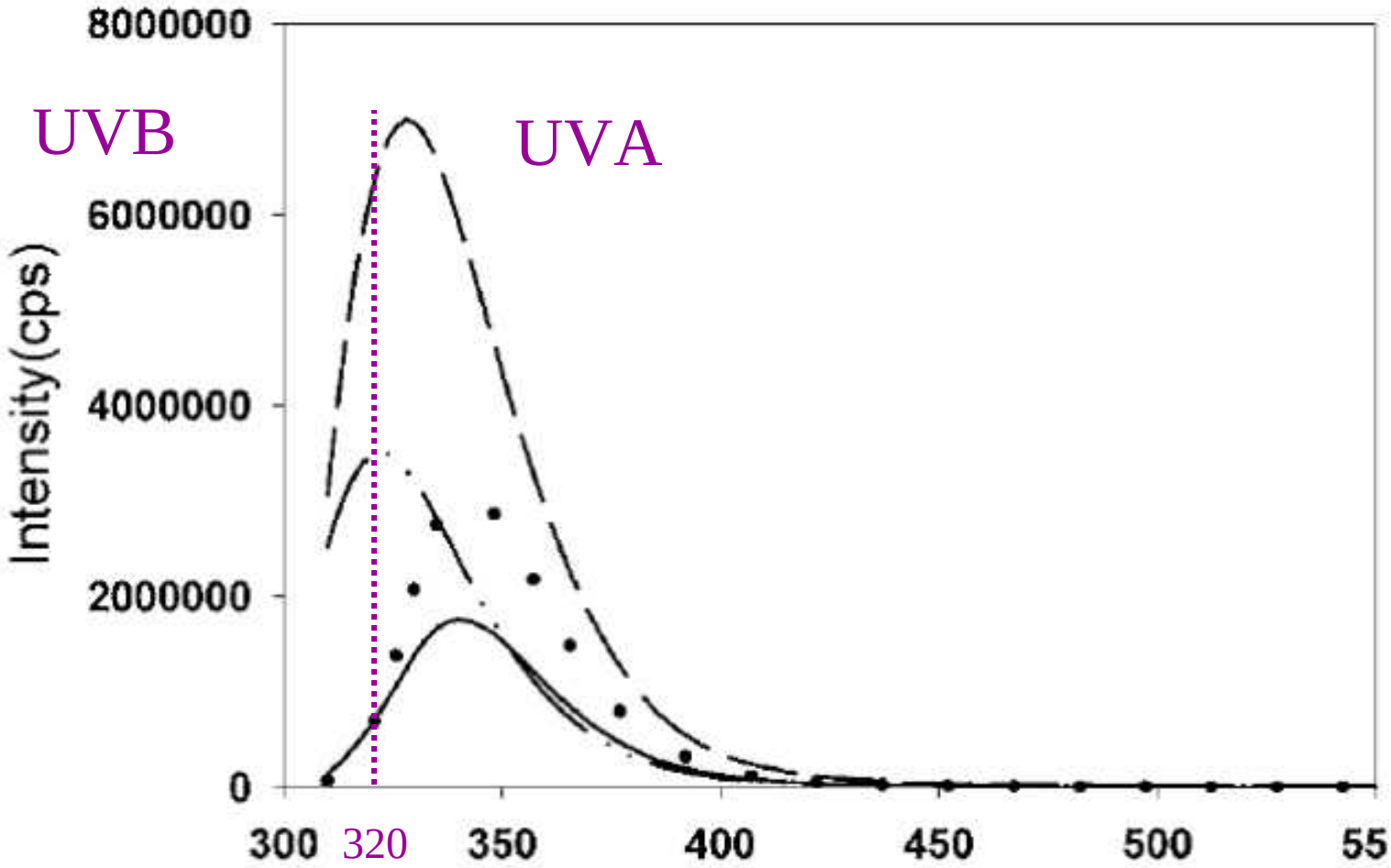
Emission spectrum of octyl methoxycinnamate in toulene (— --); ethyl acetate (– –); 1 propanol (---); and methanol (—)

Source: Krishnan R, Carr A, Blair E, Nordlund TM. Optical spectroscopy of hydrophobic sunscreen molecules adsorbed to dielectric nanospheres.Photochem Photobiol. 2004 Jun;79(6):531-9



Absorption spectrum of PABA
in toulene (— --); ethyl acetate (- -); 1 propanol (---); and methanol (—)

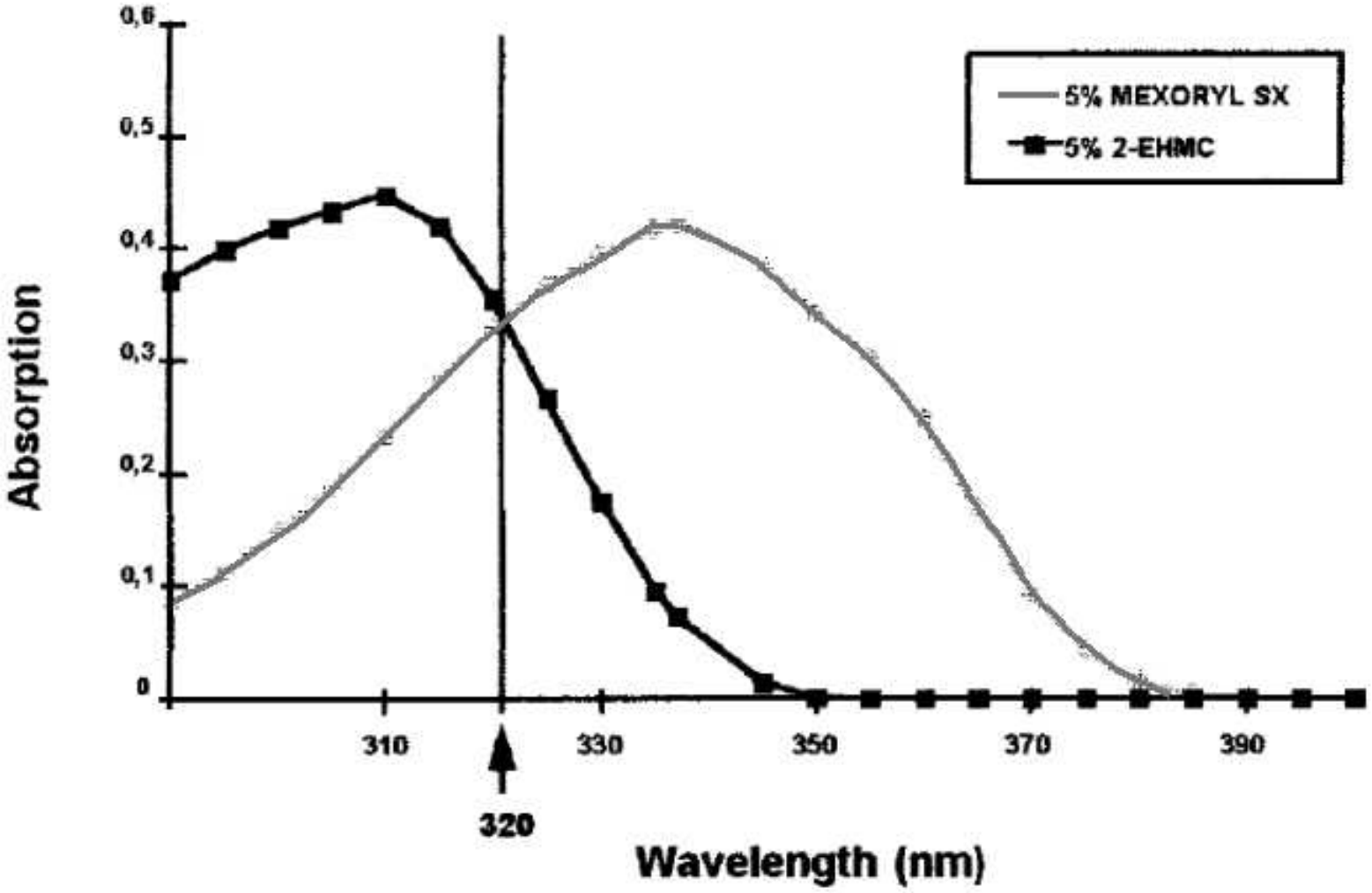
Source: Krishnan R, Carr A, Blair E, Nordlund TM. Optical spectroscopy of hydrophobic sunscreen molecules adsorbed to dielectric nanospheres.Photochem Photobiol. 2004 Jun;79(6):531-9



Emission spectrum of PABA

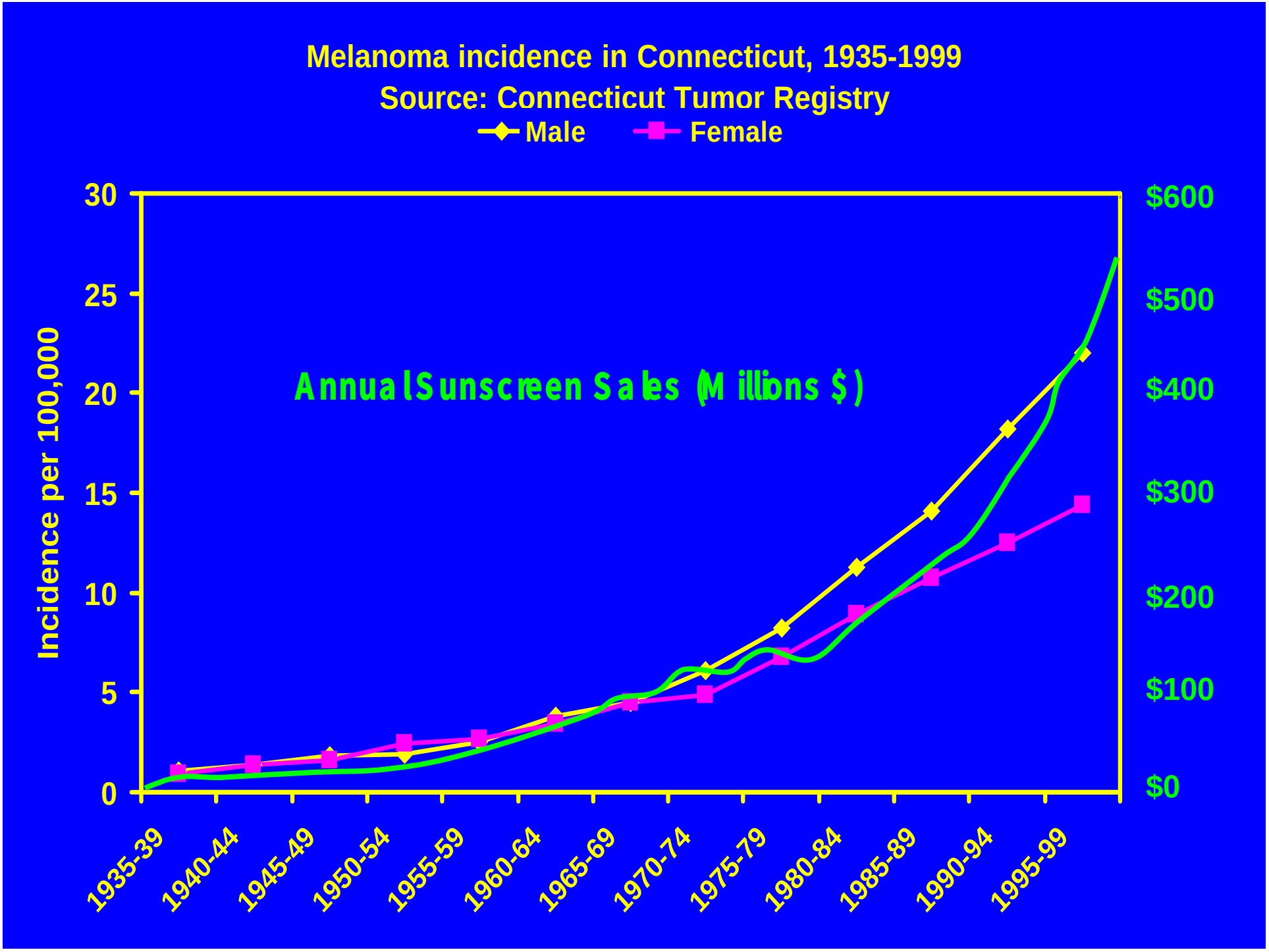
in toulene (— --); ethyl acetate (- -); 1 propanol (---); and methanol (—)

Source: Krishnan R, Carr A, Blair E, Nordlund TM. Optical spectroscopy of hydrophobic sunscreen molecules adsorbed to dielectric nanospheres.Photochem Photobiol. 2004 Jun;79(6):531-9



Absorption spectrum of 5 % Mexoryl SX and 5%2-EHMC

Source: Bernerd F, Vioux C, Asselineau D. Evaluation of the protective effect of sunscreens on in vitro reconstructed human skin exposed to UVB or UVA irradiation. Photochem Photobiol. 2000 Mar;71(3):314-20.


Melanoma incidence in Connecticut, 1935-1999
Source: Connecticut Tumor Registry
Male
Female
Annual Sunscreen Sales (Millions $)
Incidence per 100,000
30
25
20
15
10
5
0
$600
$500
$400
$300
$200
$100
$0
1935-39
1940-44
1945-49
1950-54
1955-59
1960-64
1965-69
1970-74
1975-79
1980-84
1985-89
1990-94
1995-99

American Academy of Pediatrics

For Young Children:
Apply sunscreen at least 30 minutes before going outside, and use sunscreen even on cloudy days. The SPF should be at least 15.

Potential Recommendations for Primary Prevention of Melanoma

Should we:

- Minimize UVA exposure while allowing some UVB exposure
- If skin type allows, advise10-15 minutes per day in the sun between 10:00 AM and 2:00 PM. Expose $\geq$ 40% of skin area
- In AUS , NZ, and N Europe maintain vitamin D adequacy by supplementation (1,000-2,000 IU per day, NAS No adverse effect level, 1997)
- Use only sunscreens that attenuate the entire UVA spectrum by 10-20X (probably only mixtures with TiO_2)
- Do not expect that clear sunscreens will prevent melanoma- advise hats and clothing
- Replace the erythemal SPF with a ultraviolet protection factor (UPF) that includes UVA

Gauging your Vitamin D Status

What is the best serum 25 (OH) Vitamin D concentration?

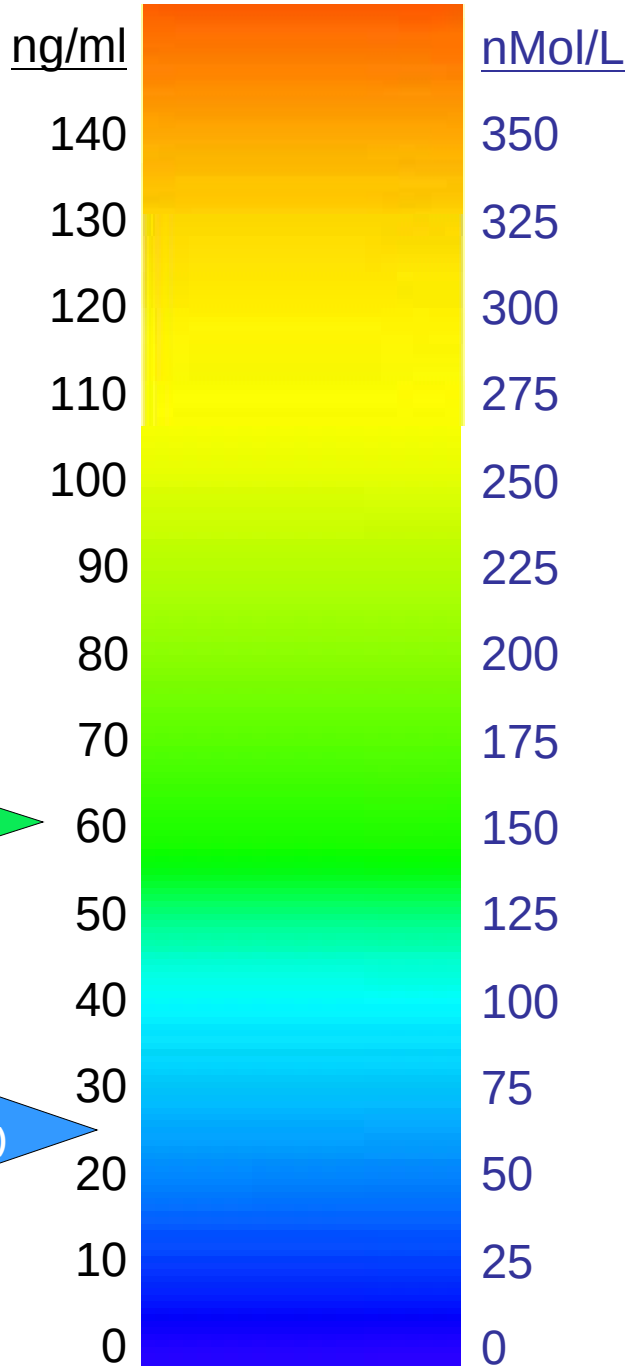
People living in sunny places with minimal clothing that doesn't limit vitamin D photosynthesis have serum 25(OH)D levels of 54 to 90 ng/ml (1).

A good target is:

60 ng/ml good target

A useful rule of thumb is that for every 100 IU of vitamin D_3 ingested, you'll gain 1 ng/mL in serum 25 (OH)D; so if your current level is 40 ng/ml you should take 2,000 IU to get up to 60 ng/ml (2).

25 ng/ml US median (NHANES 3)



1. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317-22

2. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77:204-10.

"Well, Donald – forgot your sun block, I see."